Exhibit 7

IARC MONOGRAPHS

ARSENIC, METALS, FIBRES, AND DUSTS

VOLUME 100 C
A REVIEW OF HUMAN CARCINOGENS

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

ASBESTOS (CHRYSOTILE, AMOSITE, CROCIDOLITE, TREMOLITE, ACTINOLITE, AND ANTHOPHYLLITE)

Asbestos was considered by previous IARC Working Groups in 1972, 1976, and 1987 (IARC, 1973, 1977, 1987a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series. These include the serpentine mineral chrysotile (also known as 'white asbestos'), and the five amphibole minerals – actinolite, amosite (also known as 'brown asbestos'), anthophyllite, crocidolite (also known as 'blue asbestos'), and tremolite (IARC, 1973; USGS, 2001). The conclusions reached in this *Monograph* about asbestos and its carcinogenic risks apply to these six types of fibres wherever they are found, and that includes talc containing asbestiform fibres. Erionite (fibrous aluminosilicate) is evaluated in a separate *Monograph* in this volume.

Common names, Chemical Abstracts Service (CAS) Registry numbers and idealized chemical formulae for the six fibrous silicates designated as 'asbestos' are presented in Table 1.1. Specific chemical and physical properties are also presented.

1.2 Chemical and physical properties of the agent

The silicate tetrahedron (SiO_4) is the basic chemical unit of all silicate minerals. The number of tetrahedra in the crystal structure and how they are arranged determine how a silicate mineral is classified.

Serpentine silicates are classified as 'sheet silicates' because the tetrahedra are arranged to form sheets. Amphibole silicates are classified as 'chain silicates' because the tetrahedra are arranged to form a double chain of two rows aligned side by side. Magnesium is coordinated with the oxygen atom in serpentine silicates. In amphibole silicates, cationic elements such as aluminium, calcium, iron, magnesium, potassium, and sodium are attached to the tetrahedra. Amphiboles are distinguished from one another by their chemical composition. The chemical formulas of asbestos minerals are idealized. In

Table 1.1 Common names, CAS numbers, synonyms, non-asbestos mineral analogues, idealized chemical formulae, selected physical and chemical properties of asbestos minerals

Common Name	CAS No.	Synonyms	Non-Asbestos Mineral Analogue	Idealized Chemical Formula	Colour	Decomposition Temperature (°C)	Other Properties
Asbestos	1332-21-4*	Unspecified		Unspecified			
Serpentine group of minerals							
Chrysotile	12001-29-5*	Serpentine asbestos; white asbestos	Lizardite, antigorite	$[Mg_3Si_2O_5(OH)_4]_n$	White, grey, green, yellowish	600–850	Curled sheet silicate, hollow central core; fibre bundle lengths = several mm to more than 10 cm; fibres more flexible than amphiboles; net positive surface charge; forms a stable suspension in water; fibres degrade in dilute acids
Amphibole group of minerals							
Crocidolite	12001-28-4*	Blue asbestos	Riebeckite	$[NaFe^{2+}_3Fe^{3+}_2Si_8O_{22}(OH)_2]_n$	Lavender, blue green	400–900	Double chain silicate; shorter, thinner fibres than other amphiboles, but not as thin as chrysotile; fibre flexibility: fair to good; spinnability: fair; resistance to acids: good; less heat resistance than other asbestos fibres; usually contains organic impurities, including low levels of PAHs; negative surface charge in water
Amosite	12172-73-5*	Brown asbestos	Grunerite	$[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Brown, grey, greenish	600–900	Double chain silicate; long, straight, coarse fibres; fibre flexibility: somewhat; resistance to acids: somewhat; occurs with more iron than magnesium; negative surface charge in water
Anthophyllite	77536-66-4*	Ferroanthophyllite; azbolen asbestos	Anthophyllite	$[(Mg, Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Grey, white, brown-grey, green	NR	Double chain silicate; short, very brittle fibres; resistance to acids: very; relatively rare; occasionally occurs as contaminant in talc deposits; negative surface charge in water
Actinolite	77536-67-5*	Unspecified	Actinolite	$[Ca_2(Mg, Fe^{2+})_5Si_8O_{22}(OH)_2]_n$	Green	NR	Double chain silicate; brittle fibres; resistance to acids: none; occurs in asbestiform and non-asbestiform habit; iron-substituted derivative of tremolite; common contaminant in amosite deposits; negative surface charge in water
Tremolite	77536-68-6*	Silicic acid; calcium magnesium salt (8:4)	Tremolite	$[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$	White to pale green	950–1040	Double chain silicate; brittle fibres; acid resistant; occurs in asbestiform and non-asbestiform habit; common contaminant in chrystotile and talc deposits; negative surface charge in water

* identified as asbestos by CAS Registry
NR, not reported
From ATSDR (2001), USGS (2001), HSE (2005), NTP (2005)

natural samples, the composition varies with respect to major and trace elements (USGS, 2001; HSE, 2005). More detailed information on the chemical and physical characteristics of asbestos – including atomic structure, crystal polytypes, fibre structure, chemistry and impurities – can be found in the previous *IARC Monograph* (IARC, 1973).

The structure of silicate minerals may be fibrous or non-fibrous. The terms 'asbestos' or 'asbestiform minerals' refer only to those silicate minerals that occur in polyfilamentous bundles, and that are composed of extremely flexible fibres with a relatively small diameter and a large length. These fibre bundles have splaying ends, and the fibres are easily separated from one another (USGS, 2001; HSE, 2005). Asbestos minerals with crystals that grow in two or three dimensions and that cleave into fragments, rather than breaking into fibrils, are classified as silicate minerals with a 'non-asbestiform' habit. These minerals may have the same chemical formula as the 'asbestiform' variety. (NIOSH, 2008).

Chrysotile, lizardite, and antigorite are the three principal serpentine silicate minerals. Of these, only chrysotile occurs in the asbestiform habit. Of the amphibole silicate minerals, amosite and crocidolite occur only in the asbestiform habit, while tremolite, actinolite and anthophyllite occur in both asbestiform and non-asbestiform habits (USGS, 2001; HSE, 2005; NTP, 2005).

Historically, there has been a lack of consistency in asbestos nomenclature. This frequently contributed to uncertainty in the specific identification of asbestos minerals reported in the literature. The International Mineralogical Association (IMA) unified the current mineralogical nomenclature under a single system in 1978. This system was subsequently modified in 1997 (NIOSH, 2008).

Asbestos fibres tend to possess good strength properties (e.g. high tensile strength, wear and friction characteristics); flexibility (e.g. the ability to be woven); excellent thermal properties (e.g. heat stability; thermal, electrical and acoustic insulation); adsorption capacity; and, resistance to chemical, thermal and biological degradation (USGS, 2001; NTP, 2005).

1.3 Use of the agent

Asbestos has been used intermittently in small amounts for thousands of years. Modern industrial use dates from about 1880, when the Quebec chrysotile fields began to be exploited. During the next 50 years gradual increases in production and use were reported with a cumulative total of somewhat less than 5000 million kg mined by 1930 (IARC, 1973).

As described above, asbestos has several chemical and physical properties that make it desirable for a wide range of industrial applications. By the time industrial and commercial use of asbestos peaked, more than 3000 applications or types of products were listed (NTP, 2005). Production and consumption of asbestos has declined in recent years due to the introduction of strict regulations governing exposure and/or outright bans on exposure.

Asbestos is used as a loose fibrous mixture, bonded with other materials (e.g. Portland cement, plastics and resins), or woven as a textile (ATSDR, 2001). The range of applications in which asbestos has been used includes: roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials (e.g. brake pads and shoes), coating and compounds, plastics, textiles, paper, mastics, thread, fibre jointing, and millboard (USGS, 2001; NTP, 2005; Virta, 2006). Certain fibre characteristics, such as length and strength, are used to determine the most appropriate application. For example, longer fibres tend to be used in the production of textiles, electrical insulation, and filters; medium-length fibres are used in the production of asbestos cement pipes and sheets, friction materials (e.g. clutch facings, brake linings), gaskets, and pipe coverings; and,

short fibres are used to reinforce plastics, floor tiles, coatings and compounds, and roofing felts (NTP, 2005).

Since peaking in the 1970s, there has been a general decline in world production and consumption of asbestos. Peak world production was estimated to be 5.09 million metric tons in 1975, with approximately 25 countries producing asbestos and 85 countries manufacturing asbestos products (USGS, 2001; Nishikawa *et al.*, 2008). Worldwide 'apparent consumption' of asbestos (calculated as production plus imports minus exports) peaked at 4.73 million metric tons in 1980. Asbestos cement products are estimated to have accounted for 66% of world consumption in that year (Virta, 2006). In the USA, consumption of asbestos peaked in 1973 at 719000 metric tons (USGS, 2001).

Historical trends worldwide in per capita asbestos use are presented in Table 1.2, and peak use of asbestos was higher and occurred earlier in the countries of Northern and western Europe, Oceania, and the Americas (excluding South America). Very high asbestos use was recorded in Australia (5.1 kg per capita/year in the 1970s), Canada (4.4 kg per capita/year in the 1970s), and several countries of Northern and western Europe (Denmark: 4.8 kg per capita/year in the 1960s; Germany: 4.4 kg per capita/year in the 1970s; and Luxembourg: 5.5 kg per capita/year in the 1960s) (Nishikawa *et al.*, 2008).

Current use of asbestos varies widely. While some countries have imposed strict regulations to limit exposure and others have adopted bans, some have intervened less, and continue to use varying quantities of asbestos (Table 1.2). According to recent estimates by the US Geological Survey, world production of asbestos in 2007 was 2.20 million metric tonnes, slightly increased from 2.18 million metric ton in 2006. Six countries accounted for 96% of world production in 2006: the Russian Federation (925000 metric tons), the People's Republic of China (360000 metric tons), Kazakhstan (300000 metric tons), Brazil (227304 metric tons), Canada (185000 metric tons), and Zimbabwe (100000 metric tons) (Virta, 2008). During 2000–03, asbestos consumption increased in China, India, Kazakhstan, and the Ukraine (Virta, 2006). 'Apparent' world consumption of asbestos was 2.11 million metric tons in 2003, with the Russian Federation, several former Russian states and countries in Asia being the predominant users (Virta, 2006). Consumption of asbestos in the USA (predominantly chrysotile) was 2230 metric tons in 2006, declining to 1730 metric tons in 2007 (Virta, 2008). Roofing products (includes coatings and compounds) accounted for over 80% of asbestos consumption in the USA (Virta, 2008; Virta, 2009). Asbestos products were banned in all the countries of the European Union, including Member States of eastern Europe, effective January 1, 2005 (EU, 1999).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Asbestos minerals are widespread in the environment, and are found in many areas where the original rock mass has undergone metamorphism (ATSDR, 2001; USGS, 2001). Examples include large chrysotile deposits in the Ural Mountains in the Russian Federation, in the Appalachian Mountains in the USA, and in Canada (Virta, 2006). They may occur in large natural deposits or as contaminants in other minerals (e.g. tremolite asbestos may occur in deposits of chrysotile, vermiculite, and talc). The most commonly occurring form of asbestos is chrysotile, and its fibres are found as veins in serpentine rock formations. Asbestiform amphiboles occur in relatively low quantities throughout the earth's crust and their chemical composition reflects the environment in which they form (Virta, 2002). Although most commercial deposits typically contain 5–6% of asbestos, a few deposits, such

Table 1.2 Historical trend in asbestos use per capita and status of national ban

	Use of asbestos[a] (kg per capita/year)						
Country	1950s	1960s	1970s	1980s	1990s	2000s	National ban[b]
Asia							
Israel	3.13	2.87	1.23	0.78	0.44	0.02	No ban
Japan	0.56	2.02	2.92	2.66	1.81	0.46	2004
Others[c] ($n = 39$)	0.06	0.15	0.25	0.27	0.30	0.31	3/39
Eastern Europe and Southern Europe							
Croatia	0.39	1.13	2.56	2.36	0.95	0.65	No ban
Czech Republic	1.62	2.36	2.91	2.73	1.30	0.14	2005
Hungary	0.76	1.23	2.87	3.29	1.50	0.16	2005
Poland	0.36	1.24	2.36	2.09	1.05	0.01	1997
Romania	ND	ND	1.08	0.19	0.52	0.55	2007
Spain	0.32	1.37	2.23	1.26	0.80	0.18	2002
Others[c] ($n = 15$)	0.79	1.57	2.35	2.05	2.35	1.72	5/15
Northern Europe and Western Europe							
Austria	1.16	3.19	3.92	2.08	0.36	0.00	1990
Denmark	3.07	4.80	4.42	1.62	0.09	NA	1986
Finland	2.16	2.26	1.89	0.78	ND	0	1992
France	1.38	2.41	2.64	1.53	0.73	0.00	1996
Germany	1.84	2.60	4.44	2.43	0.10	0.00	1993
Iceland	0.21	2.62	1.70	0.02	0	0.00	1983
Lithuania	ND	ND	ND	ND	0.54	0.06	2005
Luxembourg	4.02	5.54	5.30	3.23	1.61	0.00	2002
Netherlands	1.29	1.70	1.82	0.72	0.21	0.00	1994
Norway	1.38	2.00	1.16	0.03	0	0.00	1984
Sweden	1.85	2.30	1.44	0.11	0.04	NA	1986
United Kingdom	2.62	2.90	2.27	0.87	0.18	0.00	1999
Others[c] ($n = 5$)	3.05	4.32	4.05	2.40	0.93	0.05	5/5

as the Coalinga chrysotile deposits in California, USA, are reported to contain 50% or more (USGS, 2001; Virta, 2006).

1.4.2 Air

Asbestos is not volatile; however, fibres can be emitted to the atmosphere from both natural and anthropogenic sources. The weathering of asbestos-bearing rocks is the primary natural source of atmospheric asbestos. No estimates of the amounts of asbestos released to the air from natural sources are available (ATSDR, 2001). Anthropogenic activities are the predominant source of atmospheric asbestos fibres. Major anthropogenic sources include: open-pit mining operations (particularly drilling and blasting); crushing, screening, and milling of the ore; manufacturing asbestos products; use of asbestos-containing materials (such as clutches and brakes on cars and trucks); transport and disposal of wastes containing asbestos; and, demolition of buildings constructed with asbestos-containing products, such as insulation, fireproofing, ceiling and floor tiles, roof shingles, drywall, and cement (ATSDR, 2001; NTP, 2005). Concentrations of asbestos vary on a site-by-site basis and, as a result, environmental emissions are not easily estimated (ATSDR, 2001).

Table 1.2 (continued)

Country	Use of asbestos[a] (kg per capita/year)						
	1950s	1960s	1970s	1980s	1990s	2000s	National ban[b]
Americas, excluding South America							
Canada	2.76	3.46	4.37	2.74	1.96	0.32	No ban
Cuba	ND	ND	ND	0.15	0.36	0.74	No ban
Mexico	0.28	0.57	0.97	0.77	0.39	0.26	No ban
USA	3.82	3.32	2.40	0.77	0.08	0.01	No ban
Others[c] (n = 12)	0.06	0.22	0.44	0.29	0.07	0.07	0/12
South America							
Argentina	ND	0.88	0.76	0.40	0.18	0.04	2001
Brazil	0.27	0.38	0.99	1.25	1.07	0.74	2001
Chile	0.07	0.92	0.56	0.64	0.55	0.03	2001
Ecuador	ND	ND	0.67	0.52	0.14	0.26	No ban
Uruguay	ND	0.74	0.75	0.54	0.47	0.08	2002
Others[c] (n = 6)	0.27	0.43	0.60	0.47	0.29	0.19	0/6
Oceania							
Australia	3.24	4.84	5.11	1.82	0.09	0.03	2003
New Zealand	2.05	2.56	2.90	1.00	ND	ND	No ban
Others[c] (n = 3)	ND	ND	ND	ND	ND	0.22	0/3

[a] Numbers corresponding to use of asbestos by country and region were calculated as annual use per capita averaged over the respective decade.
[b] Year first achieved or year planned to achieve ban. When shown as fraction, the numerator is the number of countries that achieved bans and the denominator is the number of other countries in the region.
[c] Data on asbestos use were available (but mortality data unavailable) for others in each region, in which case data were aggregated.
ND, no data available; NA, not applicable because of negative use data; 0.00 when the calculated data were < 0.005; 0 if there are no data after the year the ban was introduced.
From Nishikawa et al. (2008)

1.4.3 Water

Asbestos can enter the aquatic environment from both natural and anthropogenic sources, and has been measured in both ground- and surface-water samples. Erosion of asbestos-bearing rock is the principal natural source. Anthropogenic sources include: erosion of waste piles containing asbestos, corrosion of asbestos-cement pipes, disintegration of asbestos-containing roofing materials, and, industrial wastewater run-off (ATSDR, 2001).

1.4.4 Soil

Asbestos can enter the soil and sediment through natural (e.g. weathering and erosion of asbestos-bearing rocks) and anthropogenic (e.g. disposal of asbestos-containing wastes in landfills) sources. The practice of disposing asbestos-containing materials in landfills was more common in the past, and is restricted in many countries by regulation or legislation (ATSDR, 2001).

1.4.5 Environmental releases

According to the US EPA Toxics Release Inventory, total releases of friable asbestos to the environment (includes air, water, and soil) in 1999 were 13.6 million pounds from 86 facilities that reported producing, processing, or using asbestos (ATSDR, 2001). In 2009, total releases of 8.9 million pounds of friable asbestos were reported by 38 facilities (US EPA, 2010).

1.5 Human exposure

Inhalation and ingestion are the primary routes of exposure to asbestos. Dermal contact is not considered a primary source, although it may lead to secondary exposure to fibres, via ingestion or inhalation. The degree of penetration in the lungs is determined by the fibre diameter, with thin fibres having the greatest potential for deep lung deposition (NTP, 2005).

1.5.1 Exposure of the general population

Inhalation of asbestos fibres from outdoor air, and to a lesser degree in indoor air, is the primary route of exposure for the non-smoking general population. Exposure may also occur via ingestion of drinking-water, which has been contaminated with asbestos through erosion of natural deposits, erosion of asbestos-containing waste sites, corrosion of asbestos-containing cement pipes, or filtering through asbestos-containing filters. Families of asbestos-workers may be exposed via contact with fibres carried home on hair or on clothing.

In studies of asbestos concentrations in outdoor air, chrysotile is the predominant fibre detected. Low levels of asbestos have been measured in outdoor air in rural locations (typical concentration, 10 fibres/m^3 [f/m^3]). Typical concentrations are about 10-fold higher in urban locations and about 1000 times higher in close proximity to industrial sources of exposure (e.g. asbestos mine or factory, demolition site, or improperly protected asbestos-containing waste site) (ATSDR, 2001). Asbestos fibres (mainly chrysotile) were measured in air and in settled dust samples obtained in New York City following destruction of the World Trade Center on September 11, 2001 (Landrigan *et al.*, 2004).

In indoor air (e.g. in homes, schools, and other buildings), measured concentrations of asbestos are in the range of 30–6000 f/m^3. Measured concentrations vary depending on the application in which the asbestos was used (e.g. insulation versus ceiling or floor tiles), and on the condition of the asbestos-containing materials (i.e. good condition versus deteriorated and easily friable) (ATSDR, 2001).

1.5.2 Occupational exposure

Asbestos has been in widespread commercial use for over 100 years (USGS, 2001). Globally, each year, an estimated 125 million people are occupationally exposed to asbestos (WHO, 2006). Exposure by inhalation, and to a lesser extent ingestion, occurs in the mining and milling of asbestos (or other minerals contaminated with asbestos), the manufacturing or use of products containing asbestos, construction, automotive industry, the asbestos-abatement industry (including the transport and disposal of asbestos-containing wastes).

Estimates of the number of workers potentially exposed to asbestos in the USA have been reported by the National Institute of Occupational Safety and Health (NIOSH), by the Occupational Safety and Health Administration (OSHA), and the Mine Safety and Health Administration (MSHA). OSHA estimated in 1990 that about 568000 workers in production and services industries and 114000 in construction industries may have been exposed to asbestos in the workplace (OSHA, 1990). Based on mine employment data from 2002, NIOSH estimated that 44000 miners and other mine workers may have been exposed to asbestos during the mining of asbestos and some mineral commodities in which asbestos may have been a potential contaminant (NIOSH, 2002b). More recently, OSHA has estimated that 1.3 million employees in construction and general industry face significant asbestos exposure on the job (OSHA, 2008). In addition to evidence from OSHA and MSHA that indicate a reduction in occupational exposures in the USA over the past several decades, other information compiled on workplace exposures to asbestos

indicates that the nature of occupational exposures to asbestos has changed (Rice & Heineman, 2003). Once dominated by chronic exposures in manufacturing process such as textile mills, friction-product manufacturing, and cement-pipe fabrication, current occupational exposures to asbestos primarily occur during maintenance activities or remediation of buildings that contain asbestos.

In Europe, estimates of the number of workers exposed to asbestos have been developed by CAREX (CARcinogen EXposure). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX database estimates that a total of 1.2 million workers were exposed to asbestos in 41 industries in the 15 Member States of the EU. Over 96% of these workers were employed in the following 15 industries: 'construction' (n = 574000), 'personal and household services' (n = 99000), 'other mining' (n = 85000), 'agriculture' (n = 81000), 'wholesale and retail trade and restaurants and hotels' (n = 70000), 'food manufacturing' (n = 45000), 'land transport' (n = 39000), 'manufacture of industrial chemicals' (n = 33000), 'fishing' (n = 25000), 'electricity, gas and steam' (n = 23000), 'water transport' (n = 21000), 'manufacture of other chemical products' (n = 19000), 'manufacture of transport equipment' (n = 17000), 'sanitary and similar services' (n = 16000), and 'manufacture of machinery, except electrical' (n = 12000). Despite the total ban of asbestos, about 1500 workers (mainly construction workers and auto mechanics) were reported as having exposure to asbestos on the Finnish Register of Workers Exposed to Carcinogens (ASA Register) in 2006 (Saalo *et al.*, 2006). In 2004, approximately 61000 workers performing demolition and reconstruction work in Germany were registered in the Central Registration Agency for Employees Exposed to Asbestos Dust (Hagemeyer *et al.*, 2006).

Exposure to asbestos in occupational settings is regulated in countries of the EU. According to the European Directive of the EC 2003/18, permissible limits are 0.1 [f/mL] for all types of asbestos, based on an 8-hour time-weighted average (8h-TWA) (EU, 2003). The same limit is in force in most Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, Newfoundland and Labrador, Prince Edward Island, New Brunswick and Nova Scotia); New Zealand; Norway; and, the USA. Other countries have permissible limits of up to 2 fibres/cm^3 (ACGIH, 2007).

Since 1986, the annual geometric means of occupational exposure concentrations to asbestos reported in the OSHA database and the MSHA database have been consistently below the NIOSH recommended exposure limit (REL) of 0.1 f/mL for all major industry divisions in the USA. The number of occupational asbestos exposure samples that were measured and reported by OSHA decreased from an average of 890 per year during 1987–94 to 241 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 6.3% during 1987–1994 to 0.9% during 1995–99. During the same two periods, the number of exposures measured and reported in the MSHA database decreased from an average of 47 per year during 1987–94 to an average of 23 per year during 1995–99. The percentage exceeding the NIOSH REL decreased from 11.1% during 1987–94 to 2.6% during 1995–99 (NIOSH, 2002a).

Data from studies and reviews of occupational asbestos exposure published since the previous *IARC Monograph* (IARC, 1973) are summarized below.

(a) Studies of occupational exposure

In a mortality study of 328 employees of an asbestos-cement factory in Ontario, Canada, Finkelstein (1983) constructed an exposure model on the basis of available air sampling data, and calculated individual exposure histories to

investigate exposure–response relationships for asbestos-associated malignancies. In retrospectively estimating exposure, the following assumptions were made: exposures did not change during 1962–70, exposures during 1955–61 were 30% higher than the later period, and exposures during 1948–54 were twice as high as during 1962–70. Exposure estimates for the years 1949, 1969, and 1979 were as follows: 40, 20, 0.2 f/mL for the willows operators; 16, 8, 0.5 f/mL for the forming machine operators; and, 8, 4, 0.3 f/mL for the lathe operators.

In an occupational hygiene survey of 24 Finnish workplaces, asbestos concentrations were measured during the different operations of brake maintenance of passenger cars, trucks and buses. During brake repair of trucks or buses, the estimated 8-hour time-weighted average exposure to asbestos was 0.1–0.2 [f/mL]. High levels of exposure (range, 0.3–125 [f/mL]; mean, 56 [f/mL]) were observed during brake maintenance if local exhaust ventilation was not used. Other operations in which the concentration exceeded 1 [f/mL] included cleaning of brakes with a brush, wet cloth or compressed air jet without local exhaust (Kauppinen & Korhonen, 1987).

Kimura (1987), in Japan, reported the following geometric mean concentrations: bag opening and mixing, 4.5–9.5 f/mL in 1970–75 and 0.03–1.6 f/mL in 1984–86; cement cutting and grinding, 2.5–3.5 f/mL in 1970–75 and 0.17–0.57 f/mL in 1984–86; spinning and grinding of friction products, 10.2–35.5 f/mL in 1970–75 and 0.24–5.5 f/mL in 1984–86.

Albin *et al.* (1990) examined total and cause-specific mortality among 1929 Swedish asbestos cement workers employed at a plant producing various products (e.g. sheets, shingles, ventilation pipes) from chrysotile and, to a lesser extent, crocidolite and amosite asbestos. Individual exposures were estimated using dust measurements available for the period 1956–77. Levels of exposure were estimated for the following operations: milling, mixing, machine line, sawing, and grinding. Asbestos concentrations ranged from 1.5–6.3 f/mL in 1956, to 0.3–5.0 f/mL in 1969, and to 0.9–1.7 f/mL in 1975. In all three time periods, the highest concentrations were observed in the milling and grinding operations.

The Health Effects Institute (1991) evaluated an operation and maintenance programme in a hospital on the basis of 394 air samples obtained during 106 on-site activities. The mean asbestos concentration was approximately 0.11 f/mL for personal samples, and approximately 0.012 f/mL for area samples. Eight-hour TWA concentrations showed that 99% of the personal samples were below 0.2 f/mL, and 95% below 0.1 f/mL.

Price *et al.* (1992) estimated the TWAs of asbestos exposures experienced by maintenance personnel on the basis of 1227 air samples collected to measure airborne asbestos levels in buildings with asbestos-containing materials. TWA exposures were 0.009 f/mL for telecommunication switch work, 0.037 f/mL for above-ceiling maintenance work, and 0.51 f/mL for work in utility spaces. Median concentrations were in the range of 0.01–0.02 f/mL.

Weiner *et al.* (1994) reported concentrations in a South African workshop in which chrysotile asbestos cement sheets were cut into components for insulation. The sheets were cut manually, sanded and subsequently assembled. Initial sampling showed personal sample mean concentrations of 1.9 f/mL for assembling, 5.7 f/mL for sweeping, 8.6 f/mL for drilling, and 27.5 f/mL for sanding. After improvements and clean-up of the work environment, the concentrations fell to 0.5–1.7 f/mL.

In a 1985 study, Higashi *et al.* (1994) collected personal and area samples at two manufacturing and processing locations in five Japanese plants manufacturing asbestos-containing products (a roofing material plant; a plant making asbestos cement sheets; a friction-material plant; and two construction and roofing-material plants). Geometric average concentrations of 0.05–0.45

f/mL were measured in area samples, and 0.05–0.78 f/mL in personal samples.

To assess the contribution of occupational asbestos exposure to the occurrence of mesothelioma and lung cancer in Europe, Albin *et al.* (1999) reviewed and summarized the available information on asbestos consumption in Europe, the proportion of the population exposed and levels of exposure. Ranges of exposure were reported for the former Yugoslavia, Poland, and Latvia. In 1987, mean fibre concentrations in Serbia and Montenegro were 2–16 f/mL for textile manufacturing, 3–4 f/mL for friction materials production, and 1–4 f/mL for asbestos cement production. In Poland, exposure levels in 1994 were estimated to be much greater than 2 f/mL in the textile industry, approximately 2 f/mL in asbestos cement and friction-products manufacturing, and greater than 0.5 f/mL in downstream use. In the Latvian asbestos cement industry in 1994, ranges of fibre concentrations were 0.1–1.1 f/mL for the machine line, and 1.1–5.2 f/mL for the milling and mixing areas.

Since 1974, NIOSH has conducted a series of sampling surveys in the USA to gather information on exposure of brake mechanics to airborne asbestos during brake repair. These surveys indicated that the TWA asbestos concentrations (about 1–6 hours in duration) during brake servicing were in the range of 0.004–0.28 f/mL, and the mean TWA concentration, approxiamtely 0.05 f/mL (Paustenbach *et al.*, 2004).

Based on a review of the historical literature on asbestos exposure before 1972 and an analysis of more than 26000 measurements collected during 1972–90, Hagemeyer *et al.* (2006) observed a continual decrease in workplace levels of airborne asbestos from the 1950s to 1990 in Western Germany (FRG) and Eastern Germany (GDR). High concentrations of asbestos fibres were measured for some working processes in Western Germany (e.g. asbestos spraying (400 [f/mL]), removal of asbestos insulations in the ship repair industry (320 [f/mL]), removal of asbestos insulation (300 [f/mL]), and cutting corrugated asbestos sheets (60 [f/mL]), see Table 1.3.

In a study at a large petroleum refinery in Texas, USA, Williams *et al.* (2007a) estimated 8h-TWA asbestos exposures for 12 different occupations (insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, laborers, and maintenance workers) from the 1940s to the 1985 onwards. Estimates were calculated using information on the historical use of asbestos, the potential for exposure due to daily work activities, occupational hygiene sampling data, historical information on task-specific exposures, and use of personal protective equipment. Exposures were estimated for 1940–50, 1951–65, 1966–71, 1972–75, 1976–85, and 1985 onwards. For these time periods, the 8h-TWA exposure (50^{th} percentile) estimates for insulators were, respectively, 9 f/mL, 8 f/mL, 2 f/mL, 0.3 f/mL, 0.005 f/mL, and < 0.001 f/mL. For all other occupations, with the exception of labourers, estimated 8h-TWA exposure estimates were at least 50- to 100-fold less than that of insulators. Estimated 8h-TWA exposure estimates for labourers were approximately one-fifth to one-tenth of those of insulators.

Williams *et al.* (2007b) reviewed historical asbestos exposures (1940–2006) in various non-shipyard and shipyard settings for the following skilled occupations: insulators, pipefitters, boilermakers, masons, welders, sheet-metal workers, millwrights, electricians, carpenters, painters, labourers, maintenance workers, and abatement workers. For activities performed by insulators in various non-shipyard settings from the late 1960s and early 1970s, average task-specific and/or full-shift airborne fibre concentrations ranged from about 2 to 10 f/mL. Average fibre concentrations in US shipyards were about 2-fold greater, and excessively high concentrations (attributed to the spraying of asbestos) were reported in some British Naval shipyards. The introduction of improved occupational hygiene

Table 1.3 Examples of asbestos fibre concentrations in the air (f/cm³) of different workplaces in Germany

Work area		1950–54[a]	1970–74	1980	1990
Textile industries	FRG	100	10	3.8	0.9
	GDR	100	12	6.2	2.2
Production of gaskets	FRG	60	6.6	4.7	0.7
	GDR	60	8.0	7.8	1.6
Production of cement	FRG	200	11	1.1	0.3
	GDR	200	13	1.9	0.7
Production of brake pads	FRG	150	9.1	1.4	0.7
	GDR	150	11	2.4	1.6
Insulation works	FRG	15	15	8.6	0.2
	GDR	18	18	14.0	0.5

[a] Data for the GDR before 1967 are extrapolated
FRG, Federal Republic of Germany; GDR, German Democratic Republic
From Hagemeyer et al. (2006)

practices resulted in a 2- to 5-fold reduction in average fibre concentrations for insulator tasks. The typical range of average fibre concentration for most other occupations was < 0.01–1 f/mL. Concentrations varied with task and time period, with higher concentrations observed for tasks involving the use of powered tools, the mixing or sanding of drywall cement, and the cleanup of asbestos insulation or lagging materials. It was not possible with the available data to determine whether the airborne fibres were serpentine or amphibole asbestos.

Madl *et al.* (2007) examined seven simulation studies and four work-site industrial hygiene studies to estimate the concentration of asbestos fibres to which workers may have historically been exposed while working with asbestos-containing gaskets and packing materials in specific industrial and maritime settings (e.g. refinery, chemical, ship/shipyard). These studies involved the collection of more than 300 air samples and evaluated specific activities, such as the removal and installation of gaskets and packings, flange cleaning, and gasket formation. In all but one of the studies, the short-term average exposures were less than 1 f/mL, and all of the long-term average exposures were less than 0.1 f/mL. Higher short-term average concentrations were observed during the use of powered tools versus hand-held manual tools during gasket formation (0.44 f/mL versus 0.1 f/mL, respectively). Peak concentrations of 0.14 f/mL and 0.40 f/mL were observed during 'gasket removal and flange face cleaning with hand tools' and 'packing removal and installation', respectively.

(b) Dietary exposure

The general population can be exposed to asbestos in drinking-water. Asbestos can enter potable water supplies through the erosion of natural deposits or the leaching from waste asbestos in landfills, from the deterioration of asbestos-containing cement pipes used to carry drinking-water or from the filtering of water supplies through asbestos-containing filters. In the USA, the concentration of asbestos in most drinking-water supplies is less than 1 f/mL, even in areas with asbestos deposits or with asbestos cement water supply pipes. However, in some locations, the concentration in water may be extremely high, containing 10–300 million f/L (or even higher). The average person drinks about 2 litres of water per day (ATSDR, 2001). Risks of exposure to asbestos in drinking-water

may be especially high for small children who drink seven times more water per day per kg of body weight than the average adult (National Academy of Sciences, 1993).

1.6 Talc containing asbestiform fibres

Talc particles are normally plate-like. These particles, when viewed on edge under the microscope in bulk samples or on air filters, may appear to be fibres, and have been misidentified as such. Talc may also form true mineral fibres that are asbestiform in habit. In some talc deposits, tremolite, anthophyllite, and actinolite may occur. Talc containing asbestiform fibres is a term that has been used inconsistently in the literature. In some contexts, it applies to talc containing asbestiform fibres of talc or talc intergrown on a nanoscale with other minerals, usually anthophyllite. In other contexts, the term asbestiform talc has erroneously been used for talc products that contain asbestos. Similarly, the term asbestiform talc has erroneously been used for talc products that contain elongated mineral fragments that are not asbestiform. These differences in the use of the same term must be considered when evaluating the literature on talc. For a more detailed evaluation of talc not containing asbestiform fibres, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.1 Identification of the agent

Talc (CAS No. 14807-96-6) is a designation for both the mineral talc and for commercial products marketed as 'talc', which contain the mineral in proportions in the range of 35% to almost 100%. Commercial talc is classified as 'industrial talc' (refers to products containing minerals other than talc), 'cosmetic talc' (refers to products, such as talcum powder, which contain > 98% talc), and 'pharmaceutical talc' (refers to products containing > 99% talc) (Rohl *et al.*, 1976; Zazenski *et al.*, 1995). Synonyms for talc include: Agalite, French chalk, kerolite, snowgoose, soapstone, steatite, talcite, and talcum.

1.6.2 Chemical and physical properties of the agent

The molecular formula of talc is $Mg_3Si_4O_{10}(OH)_2$. It is a hydrated magnesium sheet silicate mineral, whose structure is composed of a layer of $MgO_4(OH)_2$ octahedra sandwiched between identical layers of SiO_4 tetrahedra. In nature, the composition of talc varies depending on whether or not the magnesium has been substituted with other cations, such as iron, nickel, chromium or manganese (Rohl *et al.*, 1976; IMA, 2005). Pure talc is translucent, appearing white when finely ground (Zazenski *et al.*, 1995). The colour of talc changes in the presence of substituted cations, ranging from pale-green to dark-green, brownish or greenish-grey. Talc has the following chemical and physical properties: melting point, 1500°C; hardness, 1 on the Moh's scale of mineral hardness; density, 2.58–2.83; and cleavage, (001) perfect (Roberts *et al.*, 1974). Talc is a very stable mineral, and is insoluble in water, weak acids and alkalis, is neither explosive nor flammable, and has very little chemical reactivity (IMA, 2005).

Talc's structure is crystalline. It can have a small, irregular plate structure (referred to as microcrystalline talc) or it can have large, well defined platelets (referred to as macrocrystalline talc). Its platyness and crystallinity determine the specific commercial applications for which it is suitable (Zazenski *et al.*, 1995). Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition (Rohl *et al.*, 1976). Many talc-bearing rocks are formed from magnesia- and silica-rich ultramafic rocks. These rocks have a central core of serpentinite surrounded by successive shells of talc-abundant rock (e.g. talc carbonate and steatite). The serpentinite core is composed mostly of non-asbestiform serpentine minerals (lizardite

and antigorite); however, small amounts of chrysotile asbestos may occur. (Zazenski *et al.*, 1995).

More detail on the chemical and physical properties of talc can be found in the previous *IARC Monograph* (IARC, 2010).

1.6.3 Use of the agent

Talc has several unique chemical and physical properties (such as platyness, softness, hydrophobicity, organophilicity, inertness) that make it desirable for a wide range of industrial and commercial applications (e.g. paint, polymers, paper, ceramics, animal feed, rubber, roofing, fertilizers, and cosmetics). In these products, talc acts as an anti-sticking and anti-caking agent, lubricant, carrier, thickener, absorbent, and strengthening and smoothing filler (IMA, 2005).

In 2000, the worldwide use pattern for talc was as follows: paper industry, 30%; ceramics manufacture, 28%; refractories, 11%; plastics, 6%; filler or pigment in paints, 5%; roofing applications, 5%; cement, 3%; cosmetics, 2%; and other miscellaneous uses, 10% (includes agriculture and food, art sculpture, asphalt filler, autobody filler, construction caulks, flooring, and joint compounds) (Roskill Information Services Ltd, 2003). According to a Mineral Commodity Summary published by the USGS in 2009, talc produced in the USA was used for ceramics, 31%; paper, 21%; paint, 19%; roofing, 8%; plastics, 5%; rubber, 4%; cosmetics, 2%; and other, 10% (Virta, 2009).

No information on the use of asbestiform talc in various industries (apart from mining and milling of talc from deposits containing asbestiform fibres) was identified by the Working Group. For a more detailed description of the uses of talc, refer to the previous *IARC Monograph* (IARC, 2010).

1.6.4 Environmental occurrence

(a) Natural occurrence

Primary talc deposits are found in almost every continent around the world. Talc is commonly formed by the hydrothermal alteration of magnesium- and iron-rich rocks (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites (Zazenski *et al.*, 1995). For more detailed information on the formation of commercially important talc deposits, refer to the previous *IARC Monograph* (IARC, 2010).

Talc deposits whose protoliths are ultramafic rocks (or mafic) are abundant in number but small in total production. They are found in discontinuous bodies in orogenic belts such as the Alps, the Appalachians, and the Himalayas; these types of talc deposits form during regional metamorphism accompanying orogenesis. They also occur in the USA (California, Arkansas, Texas), Germany, Norway, Canada (Ontario and Quebec), southern Spain, Finland, the Russian Federation (Shabry and Miassy), and Egypt. Chlorite and amphibole are usually associated with this type of talc deposit although they are commonly separated in space from the talc ore (Vermont). The amphiboles may or may not be asbestiform, depending on the local geological history (IARC, 2010).

Talc deposits formed from the alteration of magnesian carbonate and sandy carbonate such as dolomite and limestone are the most important in terms of world production. Two types are recognized:

- those derived from hydrothermal alteration of unmetamorphosed or minimally metamorphosed dolomite such as found in Australia (Mount Seabrook and Three Springs); USA (Wintersboro, Alabama; Yellowstone, Montana; Talc City, California; Metaline Falls, Washington; and West Texas); the Republic of Korea; the People's Republic of China; India; the

Russian Federation (Onot); and, northern Spain (Respina)

- those derived from hydrothermal alteration (including retrograde metamorphism) of regionally metamorphosed siliceous dolomites and other magnesium-rich rocks such as in the USA (Murphy Marble belt, North Carolina; Death Valley-Kingston Range, California; Gouverneur District, New York; Chatsworth, Georgia); Canada (Madoc); Italy (Chisone Valley); the Russian Federation (Krasnoyarsk); Germany (Wunsiedel); Austria (Leoben); Slovakia (Gemerska); Spain; France (Trimouns); and Brazil (Brumado) (IARC, 2010).

In a study to examine the amphibole asbestos content of commercial talc deposits in the USA, Van Gosen *et al.* (2004) found that the talc-forming environment (e.g. regional metamorphism, contact metamorphism, or hydrothermal processes) directly influenced the amphibole and amphibole-asbestos content of the talc deposit. Specifically, the study found that hydrothermal talcs consistently lack amphiboles as accessory minerals, but that contact metamorphic talcs show a strong tendency to contain amphiboles, and regional metamorphic talc bodies consistently contain amphiboles, which display a variety of compositions and habits (including asbestiform). Death Valley, California is an example of a contact metamorphic talc deposit that contains accessory amphibole-asbestos (namely talc-tremolite).

1.6.5 Human exposure

(a) Exposure of the general population

Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powders) are the primary routes of exposure. As talc is used as an anti-sticking agent in several food preparations (e.g. chewing gum), ingestion may also be a potential, albeit minor, route of exposure.

As late as 1973, some talc products sold in the USA contained detectable levels of chrysotile asbestos, tremolite, or anthophyllite (Rohl *et al.*, 1976), and it is possible that they remained on the market in some places in the world for some time after that (Jehan, 1984). Some of the tremolite and anthophyllite may have been asbestiform in habit (Van Gosen, 2006).

Blount (1991) examined pharmaceutical- and cosmetic-grade talcs for asbestiform amphibole content using a density-optical method. High-grade talc product samples (n = 15) were collected from deposits in Montana, Vermont, North Carolina, Alabama, and from outside the USA but available in the US market. Samples were uniformly low in amphibole content (with counts in the range of 0–341 particles/mg), and some samples appeared to be completely free of amphibole minerals. In samples containing amphibole minerals, cleavage-type and asbestos-type minerals were observed. Only one sample was found to contain an amphibole particle size distribution typical of asbestos.

More complete information on the levels of exposure experienced by the general population can be found in the previous *IARC Monograph* (IARC, 2010).

(b) Occupational exposure

Inhalation is the primary route of exposure to talc in occupational settings. Exposure by inhalation to talc dust occurs in the talc-producing industries (e.g. during mining, crushing, separating, bagging, and loading), and in the talc-using industries (e.g. rubber dusting and addition of talcs to ceramic clays and glazes). Because industrial talc is a mixture of various associated minerals, occupational exposure is to a mixture of mineral dusts (IARC, 1987b).

In general, data on numbers of workers occupationally exposed to talc are lacking. The

National Occupation Exposure Survey (NOES), which was conducted by the US National Institute for Occupational Safety and Health (NIOSH) during 1981–83, estimated that 1.4 million workers, including approximately 350000 female workers, were potentially exposed to talc in the workplace (NIOSH, 1990). CAREX reports that approximately 28000 workers were exposed to talc containing asbestiform fibres in the workplace within the 15 countries that comprised the EU during 1990–93; however, some major industries producing or using talc were not included.

Many of the early measurements reported very high levels of talc dust exposures in mining and milling operations, often in the range of several mg/m^3, but there is evidence of decreasing exposures (IARC, 1987b; IARC, 2010). For example, before the adoption of technical preventive means in 1950, exposures in the talc operation in the Germanasca and Chisone Valley (Piedmont), Italy, were reported to be approximately 800 mppcf in the mines, and approximately 25 mppcf in the mills. Exposures in both areas were reduced to less than 10 mppcf after 1965 when improved occupational hygiene practices were implemented (Rubino *et al.*, 1976). Although the presence of asbestiform talc was often not reliably verified, it is likely that these levels have also decreased, in part due to mine closures and regulatory controls.

Oestenstad *et al.* (2002) developed a job–exposure matrix for respirable dust, covering all work areas in an industrial grade (tremolitic) talc mining and milling facility in upstate New York, USA. The facility started operating in 1948 with the opening of an underground mine (Mine 1) and a mill (Mill 1). An open pit mine (Mine 2) opened in 1974. Talc from the facility was used predominantly for manufacturing paint and ceramic tiles. The range of all respirable dust concentrations measured in the two baseline exposure surveys was 0.01–2.67 mg/m^3, with an arithmetic mean of 0.47 mg/m^3 and a geometric mean of 0.28 mg/m^3.

Only limited information is available about exposures in secondary industries in which talc is used or processed further. The previous *IARC Monograph* on talc (IARC, 2010) summarizes three historical surveys conducted in these kinds of industries. The IARC Working Group in 1987 noted, however, that even when measurements of respirable fibres were reported, no electron microscopic analysis was conducted to confirm the identity of the fibres. Recently, most industries using talc use non-asbestiform talc (IARC, 2010).

For a more complete description of studies in which occupational exposure to talc and talc-containing products has been reported, refer to the previous *IARC Monograph* (IARC, 2010).

2. Cancer in Humans

2.1 Introduction

The previous *IARC Monographs* were limited to the same six commercial forms of asbestos fibres (chrysotile, actinolite, amosite, anthophyllite crocidolite and tremolite) that are subject of this current evaluation. In the previous *IARC Monograph* (IARC, 1977), the epidemiological evidence showed a high incidence of lung cancer among workers exposed to chrysotile, amosite, anthophyllite, and with mixed fibres containing crocidolite, and tremolite. Pleural and peritoneal mesotheliomas were reported to be associated with occupational exposures to crocidolite, amosite, and chrysotile. Gastrointestinal tract cancers were reported to have been demonstrated in groups occupationally exposed to amosite, chrysotile or mixed fibres containing chrysotile. An excess of cancer of the larynx in occupationally exposed individuals was also noted. Finally the *Monograph* points out that mesothelioma may occur among individuals living in neighbourhoods of asbestos factories

and crocidolite mines, and in persons living with asbestos workers.

Extensive epidemiological research on asbestos has been conducted since then. The associations between asbestos exposure, lung cancer, and mesothelioma have been well established in numerous epidemiological investigations. The epidemiological evidence for other cancer sites is less extensive than it is for lung cancer and mesothelioma, but is still considerable for some. In reviewing these studies, there are some common limitations that need to be borne in mind, which may explain the heterogeneity of the findings from the studies such as:

- The types, fibre sizes and levels of asbestos exposure differed from industry to industry and over time. Most of the heaviest exposures probably occurred in the first two-thirds of the twentieth century in asbestos mining and milling, insulation work, shipyard work, construction, and asbestos textile manufacture. Workers in different industries, eras, and geographic locales were exposed to different types of asbestos fibres, and to fibres of greatly varying dimensions.
- There were differences in how the studies handle the issue of latency or in other words time since first occupational exposure to asbestos. Some studies, especially earlier investigations, accumulated person–years from first exposure, a procedure that may dilute observed risk by including many years of low risk. Others have only accumulated person–years after a certain period of time after first exposure, usually 20 years. Also different studies followed their populations for very different periods of time since first occupational exposure to asbestos.
- The most pervasive problem in interpreting studies was the wide variation among studies in the approaches taken for exposure assessment. Some studies made no attempt to assess exposure beyond documenting employment of study participants in a trade or industry with potential for occupational exposure to asbestos. Other studies used surrogate indices of exposure such as duration of employment or self-reported intensity of exposure, or stratified subjects' exposure by job title. Some used the skills and knowledge of industrial hygienists, obtained direct measurements of asbestos dust levels in air, and developed job–exposure matrices and cumulative exposure indices. Even these analyses are limited by the fact that earlier studies used gravimetric measures of dust exposure, while later used fibre-counting methods based on phase contrast microscopy (PCM). Factors that were used to convert between gravimetric and PCM based measurements are generally unreliable unless they are based on side by side measurements taken in specific industrial operations. Differences in fibre size distributions and fibre type can only be detected using electron microscopy, which has been done in only a very few studies.
- Misclassification of disease was a serious problem for several of the cancer sites. This is particularly true for mesothelioma, which did not have diagnostic category in the ICD system until the 10th review was initiated in 1999.

There were also issues regarding the potential for misclassification of mesotheliomas as colon or ovarian cancers.

For talc that contains asbestiform fibres, previous Working Groups assessed studies on talc described as containing asbestiform tremolite and anthophyllite (IARC, 1987a, b). These fibres fit the definition of asbestos, and therefore a separate review of talc containing asbestiform fibres was not undertaken by this Working Group. The reader is invited to consult the General Remarks

in this volume for further details. For a review of Talc, refer to the previous *IARC Monograph* (IARC, 2010).

2.2 Cancer of the lung

2.2.1 Occupational exposure

Signs that cancer of the lung could be induced by exposure to asbestos was first raised by reports of lung cancer cases that occurred among workers with asbestosis (Gloyne, 1935; Lynch & Smith, 1935). The first cohort study that demonstrated an excess of lung cancer among asbestos exposed workers was a study of textile workers (Doll, 1955). In this study, 11 cases of lung cancer versus 0.8 expected ($P < 0.00001$) were reported based on national mortality rates. Since 1955, an association between lung cancer and occupational exposure to asbestos has been demonstrated in numerous cohort and case–control studies that are summarized in Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.1.pdf, Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.2.pdf, and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.3.pdf.

Although a causal association between asbestos exposure and lung cancer is generally well recognized, there are still substantial controversies on how the risk might vary by exposure to different fibre types and sizes, and whether there is a risk at low levels of exposure (i.e. environmental exposures). Particularly controversial is the question of whether chrysotile asbestos is less potent for the induction of lung cancer than the amphibole forms of asbestos (e.g. crocidolite, amosite and tremolite), which has sometimes been referred to as the "amphibole hypothesis" (Cullen, 1996; Stayner *et al.*, 1996; McDonald, 1998). This argument is based on the observation from experimental studies that chrysotile asbestos is less biopersistent (i.e. has a shorter half life) in the lung than the amphiboles. Pathological studies of tissue using electron microscopy and energy dispersive analysis of X-rays (EDAX) have been used to measure the amounts of different asbestos fibre types in the lung. Case studies of Canadian chrysotile asbestos workers using these methods have shown an unexpectedly high proportion of amphibole (primarily tremolite) fibres, considering the relatively low percentage of amphibole fibres in commercial chrysotile asbestos (Pooley, 1976; Rowlands *et al.*, 1982; Addison & Davies, 1990). [The Working Group noted that the lower biopersistence of chrysotile in the lung does not necessarily imply that it would be less potent than amphiboles for lung cancer.]

Several meta-analyses have been conducted in which the relative potency of different fibre types and other fibre characteristics have been considered in relation to lung cancer. Lash *et al.* (1997) conducted a meta-analysis based on the findings from 15 cohort studies with quantitative information on the relationship between asbestos exposure and lung cancer risk. The slopes of the lung cancer exposure–response relationship from these studies were analysed using fixed and random effects models. Substantial heterogeneity in the slopes for lung cancer from these studies was found in their analysis. The heterogeneity was largely explained by industry category, dose measurements, tobacco habits, and standardization procedures. There was no evidence in this meta-analysis that differences in fibre type explained the heterogeneity of the slope.

Hodgson & Darnton (2000) performed a meta-analysis based on 17 cohort studies with information on the average level of asbestos exposure for the cohort as a whole or for subgroups in the study. The percentage excess lung cancer risk from each study or subgroup was divided by its average exposure level to derive a slope (RL) for the analysis. Substantial heterogeneity in the findings for lung cancer was also found in this

analysis particularly for the chrysotile cohorts. The heterogeneity in the findings for the chrysotile cohorts was largely attributable to differences in the findings from the studies of chrysotile miners and millers in Quebec (McDonald *et al.*, 1983), and asbestos textile workers in South Carolina (Dement & Brown, 1994; Hein *et al.*, 2007), which differed by nearly 100-fold. No explanation has been found for these extreme differences although several possible explanations have been investigated. Co-exposure to mineral oils in the South Carolina textile plant was proposed as a possible explanation. A nested case–control conducted with the South Carolina cohort failed to provide evidence to support the hypothesis that mineral exposure was associated with an increased risk of lung cancer in this study population (Dement & Brown, 1994). Differences in fibre size distributions have also been considered to be a potential explanation. The asbestos textile industry workers may have used a higher grade of asbestos resulting in exposures to a greater percentage of long fibres than what was experienced by miners and millers in Quebec. A larger percentage of long fibres was found in a recent reanalysis of samples from the South Carolina cohort using transmission electron microscopy (TEM) (Dement *et al.*, 2008) than what was previously reported in TEM analyses of samples from the Quebec mines and mills (Gibbs & Hwang, 1975, 1980). Based on their analysis, Hodgson & Darnton (2000) concluded that the ratio between lung cancer risk for chrysotile and the amphiboles was somewhere between 1:10 and 1:50. However, in their analyses (where they excluded the study of Quebec miners rather than the South Carolina cohort), there was only a 2-fold difference in findings for lung cancer risk between the chrysotile (RL = 2.3) and amphibole cohorts (RL = 4.2). [The Working Group noted that there is no justification for exclusion of the South Carolina cohort because it is one of the highest quality studies in terms of the exposure information used in this study.]

Berman & Crump (2008a) published a meta-analysis that included data from 15 asbestos cohort studies. Lung cancer risk potency factors (Kis = [RR-1]/cumulative exposure) were derived in their analyses that were specific for both fibre type (chrysotile versus amphiboles) and fibre size (length and width). Fibre size information was only available for one of the cohort studies, and for the other studies it was obtained from studies that were conducted in similar industrial settings. As with the previous analyses, substantial variation was found in the findings from these studies with results for lung cancer varying by two orders of magnitude, although no formal statistical tests of heterogeneity were performed. The hypothesis that chrysotile is equipotent as the amphiboles for lung cancer was not rejected for fibres of all widths ($P = 0.07$) or for thick (width > 0.2 μm) fibres ($P = 0.16$). For thin fibres (width < 0.2 μm), there was significant ($P = 0.002$) evidence that chrysotile fibres were less potent than amphiboles. Sensitivity analyses were also conducted in which the South Carolina or Quebec miners and millers cohorts were dropped from the analysis using fibres of all widths. Dropping the South Carolina cohort resulted in a highly significant ($P = 0.005$) result that potency was greater for amphiboles than for chrysotile. Dropping the Quebec cohort resulted in there being no significant ($P = 0.55$) evidence of a difference in potency between the fibre types. [The Working Group noted that both the Hodgson & Darnton and Berman & Crump analyses reveal a large degree of heterogeneity in the study findings for lung cancer, and that findings are highly sensitive to the inclusion or exclusion of the studies from South Carolina or Quebec. The reasons for the heterogeneity are unknown, and until they are explained it is not possible to draw any firm conclusions concerning the relative potency of chrysotile and amphibole asbestos fibres from these analyses.]

Based on findings from experimental studies, it is suspected that long and thin fibres are likely

to be more potent than short and thick fibres in the induction of lung cancer in humans. Unfortunately until recently, all of the epidemiological studies that have been conducted used methods for exposure assessment that did not include a determination of fibre size, and thus this issue could not be directly addressed with these studies. As described above, the meta-analysis conducted by Berman & Crump (2008a) considered the effect of fibre size on lung cancer risk by using data from other studies conducted in similar circumstances as the cohort studies. Their analysis did not reveal strong evidence that lung cancer potency was dependent on fibre size. There was weak evidence that long fibres (length > 10 μm) were more potent than short fibres (5 μm < length < 10 μm) in models using all widths ($P = 0.07$). The lack of size-specific data from the studies was a major limitation of this study with regard to estimating size-specific risk estimates. Stayner *et al.* (2008) published findings from an analysis of the South Carolina asbestos textile cohort in which fibre size specific estimates of lung cancer mortality was evaluated using information from a reanalysis of archived air samples using TEM (Dement *et al.*, 2008). Long fibres (> 10 μm) and thin fibres (< 0.25 μm) were found to be the strongest predictors of lung cancer mortality in this study.

Another study not part of the prior meta-analyses provides relevant information regarding the question of the relative lung cancer potency of the fibre types. Loomis *et al.* (2009) carried out a retrospective cohort mortality study of textile workers from four plants in North Carolina that had never been studied before. Workers in this cohort were primarily exposed to chrysotile asbestos that was imported from Quebec. A small amount of amosite was used in an operation in one of the plants. Overall, an excess of lung cancer was observed in this study (SMR, 1.96; 95%CI: 1.73–2.20), which was very similar in magnitude to that reported in the South Carolina cohort study of textile workers (Hein *et al.*, 2007). However, the slope for the exposure–response between asbestos exposure and lung cancer was considerably lower than that reported in the South Carolina cohort study. The reasons for these differences in the exposure–response relationships are unknown, but one possible reason may be that quality of the exposure information was superior in the South Carolina study, and that the difference could be explained by an attenuation of the slope due to exposure misclassification in Loomis *et al.* (2009).

2.2.2 Environmental exposures

Evidence of an association in women between lung cancer and environmental exposures in New Caledonia to field dust containing tremolite and the use of a whitewash ("po") containing tremolite has been reported (Luce *et al.*, 2000). A positive association with heavy residential exposure to asbestos was observed in a lung cancer case–control study the Northern Province of South Africa, which is a crocidolite and amosite mining area (Mzileni *et al.*, 1999). The association was strongest among women who resided in heavily exposed areas (odds ratio [OR], 5.4; 95%CI: 1.3–22.5; Ptrend = 0.02). A study of lung cancer mortality among women in two chrysotile mining regions of Quebec did not result in an increase in lung cancer (SMR, 0.99; 95%CI: 0.78–1.25) relative to women from 60 other areas of Canada (Camus *et al.*, 1998).

2.2.3 Non-commercial asbestiform amphibole fibres

There is emerging epidemiological evidence that non-commercial amphibole fibres that are asbestiform have carcinogenic potential. These fibres are not technically "asbestos," and they were never commercially marketed. However, the Working Group felt it was important to discuss the recent evidence concerning these

fibres because of their similarity to asbestos, and because of public concerns regarding this issue.

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a), however, they have been more recently described by the US Geological Society as approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported standardized mortality ratios (SMRs), using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs for all cancer (SMR, 1.4; 95%CI: 1.2–1.6; $n = 202$), and lung cancer (SMR, 1.7; 95%CI: 1.4–2.1; $n = 89$). Increasing risks were observed across categories of cumulative exposure; the SMR estimates were 1.5, 1.6, 1.8, and 1.9 in the 1–4.49, 4.5–22.9, 23.0–99.0, and ≥ 100 f/mL–years exposure categories, respectively. Results from other studies (Amandus *et al.*, 1987; McDonald *et al.*, 2004) of analyses using a continuous measure of exposure also resulted in statistically significant relationships with lung cancer mortality risk. For example, in the updated analysis by McDonald *et al.* (2004), the estimated linear increase in relative risk of respiratory cancer risk per 100 f/mL–years cumulative exposure was 0.36 (95%CI: 0.03–1.2; $P = 0.02$).

2.3 Mesothelioma

Pleural and peritoneal mesotheliomas are very rare malignancies that occur in the mesothelial cells that line these cavities. The first report of a possible association between asbestos exposure and mesothelioma was by Wagner *et al.* (1960) who described an outbreak of mesothelioma in a crocidolite mining region of South Africa. The majority of the cases reported had worked in the mines (23/33) but some of the cases had also occurred among individuals with no history of occupational exposures (10/33). Since then, an excess of mesothelioma has been observed in a large number of cohort and case–control studies (summarized in online Tables 2.2, 2.3 and Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.4.pdf) in a variety of different industries using and producing asbestos. Although the causal association between mesothelioma and asbestos has been well established, several important issues remain to be resolved that are discussed below.

2.3.1 Fibre type

Although all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos. An excess of mesothelioma has been reported in cohort studies of chrysotile exposed miners and millers in Quebec (Liddell *et al.*, 1997), and in South Carolina asbestos textile workers who were predominantly exposed to chrysotile asbestos imported from Quebec (Hein *et al.*, 2007). However, the fact that the chrysotile asbestos mined in Quebec is contaminated with a small percentage (< 1.0%) of amphibole (tremolite) asbestos has complicated the interpretation of these findings. McDonald *et al.* (1997) found in a nested case–control study for mesothelioma in the Thetford mines of Quebec that an association with asbestos exposure was evident in mines from a region with higher concentrations of tremolite, and not in another region with lower concentrations of tremolite. Bégin *et al.* (1992) noted that although tremolite levels may be 7.5 times higher in Thetford than in Asbestos, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their workforce. This suggests that the tremolitic content of the ores may not be a

determinant of mesothelioma risk in Quebec. Separate analyses for workers at the Thetford and Asbestos mines and mills did not demonstrate a different exposure–response relationship for asbestos and mesothelioma in the two mining areas (McDonald & McDonald, 1995).

In a mesothelioma case–control study in South Africa, an association was reported with exposures to crocidolite and amosite asbestos, but no cases were found to have been exclusively exposed to chrysotile asbestos (Rees *et al.*, 1999). One possible explanation for these negative findings for chrysotile is that South African chrysotile asbestos may contain relatively little tremolite (Rees *et al.*, 1992). Another possible explanation is that chrysotile mining began later, and production levels were lower than in the crocidolite and amosite mines of South Africa. Cases of mesothelioma have been reported among asbestos miners in Zimbabwe, which has been reported to be uncontaminated with tremolite asbestos (Cullen & Baloyi, 1991). Excess mesothelioma mortality (standardized incidence ratio [SIR], 4.0, 95%CI: 1.5–8.7) was reported in miners and millers from a chrysotile mine in Balangero, Italy (Mirabelli *et al.*, 2008), reportedly free of amphibole contamination (Piolatto *et al.*, 1990).

An evaluation of the relative potency of the different fibre types of asbestos has been considered in the meta-analyses that were previously described (see prior section on lung cancer) by Hodgson & Darnton (2000) and Berman & Crump (2008a, b). Hodgson & Darnton (2000) used the percentage of mesothelioma deaths of all deaths expected (at an age of first exposure of 30) per unit of cumulative exposure (Rm) as the measure for their analysis. They computed separate estimates of Rm for crocidolite, amosite and chrysotile asbestos. Based on their analyses, they estimated that the ratio of the potency for mesothelioma (pleural and peritoneal combined) was 1:100:500 for chrysotile, amosite, and crocidolite respectively.

The meta-analysis conducted by Berman & Crump (2008a) was based on the analysis of the slopes (Km) that were estimated using an approach that assumes that the mortality rate from mesothelioma increases linearly with the intensity of exposure, and for a given intensity, increases indefinitely after exposure ceases, approximately as the square of time since first exposure (lagged 10 years). This model was tested with the raw data from several studies, and found to provide a good fit to the data (Berman & Crump, 2008b). Regression models were fitted to the study Km values that included information from surrogate studies to estimate fibre type (chrysotile versus amphiboles) and fibre length (short versus long) specific potency slopes (Berman & Crump, 2008a). Alternative models were fitted with exposure metrics based on different fibre widths. The hypothesis that chrysotile and amphibole forms of asbestos are equipotent was strongly rejected, and the hypothesis that potency for chrysotile asbestos was 0 could not be rejected based on their models ($P < 0.001$ and $P = 0.29$, respectively, for all-widths model). The best estimates for the relative potency of chrysotile ranged from zero to about 1/200th that of amphibole asbestos (depending on the width of the exposure metric used in the model). [The Working Group noted that there is a high degree of uncertainty concerning the accuracy of the relative potency estimates derived from the Hodgson & Darnton and Berman & Crump analyses because of the severe potential for exposure misclassification in these studies.]

Two newer studies, not part of the prior meta-analyses, provide important information regarding the question of the relative potency of the fibre types. The first is a study of a cohort of textile workers in North Carolina not previously examined (Loomis *et al.*, 2009). Workers in this cohort were primarily exposed to chrysotile asbestos imported from Quebec. A relatively large excess of both mesothelioma [SMR, 10.92; 95%CI: 2.98–27.96] and pleural cancer [SMR,

12.43; 95%CI: 3.39–31.83]. The pleural and mesothelioma deaths combined comprised 0.3% of all deaths. This percentage was nearly identical to the estimate developed for the chrysotile cohorts in a review article by Stayner *et al.* (1996). Based on the approach that Hodgson & Darnton used in their meta-analysis, the authors estimated that the percentage of deaths per unit of fibre exposure was 0.0058% per f–y/mL (0.0098% per f–y/mL for workers followed ≥ 20 years). This estimate was considerably higher than the estimate developed by Hodgson & Darnton of 0.0010% per f–yr/mL for cohorts exposed to chrysotile.

The other study investigated mesothelioma among chrysotile miners and millers, and resident communities in Balangero, Italy. The chrysotile mined at Balangero was reported to be free of tremolite and other amphiboles. The ore contains trace amounts of another fibre called blangeroite, which is not an amphibole (Turci *et al.*, 2009). A previous cohort of the miners and millers in Balangero with follow up to 1987 identified only two deaths from mesothelioma (Piolatto *et al.*, 1990). Cases of mesothelioma were identified from a local mesothelioma registry comprises people who had been mine employees; employees of subcontractors or other firms transporting or refining Balangero asbestos, asbestos ore; residents of the area who were exposed from air pollution, living with a mine employee or from mine tailings from Balangero. Six cases of mesothelioma were identified among blue-collar miners, and an estimated 1.5 deaths (SIR, 4.00; 95%CI: 1.47–8.71) would be expected based on a previous cohort study (Piolatto *et al.*, 1990), and conservative assumptions about the cohort. Additional cases of mesothelioma were identified among white-collar miners (three cases), workers in the mine hired by subcontractors (five cases), and from non-occupational exposures or exposure to re-used tailings (ten cases). Expected numbers of mesothelioma cases could not be derived for these groups because they were not part of the original cohort definition. The findings from this investigation indicate that the previous risk of mesothelioma for the Balangero cohort were seriously underestimated.

2.3.2 Fibre size

Based on a review of toxicological and human studies, Lippmann (1990) suggested that fibres shorter than 0.1 µm and longer than 5 µm are related to mesothelioma in humans. The Berman & Crump meta-analyses provided weak evidence that fibre length is a determinant of the potency of asbestos. The test of the hypothesis that long fibres (length ≥ 10 µm) and short fibres (5 < length < 10 µm) are equipotent was nearly rejected in some models (e.g. $P = 0.09$ for all widths). Thus, their findings provide weak support that long fibres may be more potent than short fibres for mesothelioma. There was little evidence in their analyses that thin fibres (width < 0.4 or < 0.2 µm) were stronger predictors of mesothelioma potency than all fibre widths combined. A major limitation of their analysis was that it relied on surrogate data to estimate the fibre-size distributions for the studies used in the meta-analysis.

2.3.3 Pleural versus peritoneal tumours

The ratio of pleural to peritoneal mesotheliomas has varied considerably in different epidemiological studies of asbestos-exposed cohorts. In the cohort studies included in the meta-analysis conducted by Hodgson & Darnton (2000), the percentage of mesotheliomas that were peritoneal varied from 0 to over 50%. Hodgson & Darnton reported that peritoneal mesotheliomas increased with the square of cumulative exposure to asbestos (i.e. a supralinear relationship); whereas pleural mesotheliomas increased less than linearly with cumulative exposure to asbestos. This implies that the number of peritoneal mesotheliomas would dramatically increase relative to the number of pleural mesotheliomas at high asbestos exposure levels. Welch *et al.*

(2005) found a strong association (OR, 5.0; 95%CI: 1.2–21.5) between asbestos exposure and peritoneal cancer in a population-based case–control study. This study included a large percentage of men with what were judged to be low exposures to asbestos.

2.3.4 Environmental exposures

An excess of mesothelioma has been observed in several studies of communities with environmental exposure to asbestos. A large excess of mesothelioma was reported in a study of people living in villages in Turkey exposed to erionite used to whitewash their homes (Baris *et al.*, 1987). An excess in mesothelioma was reported among people living near crocidolite mining regions in South Africa and Western Australia (Wagner & Pooley, 1986), among people residing in areas of tremolite contamination in Cyprus (McConnochie *et al.*, 1987) and New Caledonia (Luce *et al.*, 2000), and with non-occupational exposures in Europe (Magnani *et al.*, 2000), Italy (Magnani *et al.*, 2001), and California (Pan *et al.*, 2005).

Mesothelioma has also been reported to occur among household members of families of asbestos workers (Anderson *et al.*, 1976; Ferrante *et al.*, 2007).

2.3.5 Non-commercial asbestiform fibres

Several studies have described adverse health associations with the amphibole fibres that contaminated vermiculite mined in Libby, Montana, USA. These fibres were originally characterized as from the tremolite-actinolite series (IARC, 1987a); however, they were subsequently described by the US Geological Society as being composed of approximately 84% winchite, 11% richterite, and 6% tremolite (Meeker *et al.*, 2003). Sullivan (2007) reported SMRs, using cause of death data and expected mortality for the underlying cause of death based on national age-, race-, and sex-specific rates. Using a 15-year exposure lag, there were increased SMRs, mesothelioma defined by ICD-10 for deaths after 1999 (SMR, 14.1; 95%CI: 1.8–54.4; n = 2) and pleural cancer (SMR, 23.3; 95%CI: 6.3–59.5; n = 4). The only exposure–response modelling of mesothelioma was presented in the paper by McDonald *et al.*, based on 12 mesothelioma cases (McDonald *et al.*, 2004). Using Poisson regression, the mesothelioma mortality rate across increasing categories of exposure was compared with the rate in the lowest exposure category. For the cumulative exposure metric, the relative risk estimates were 1.0 (referent), 3.72, 3.42, and 3.68, based on 1, 4, 3, and 4, cases, respectively. The mean exposure level in these four quartiles was 8.6, 16.7, 53.2, and 393.8 f/mL–yr, respectively. It should be noted that the referent group was also at excess risk of dying from mesothelioma, i.e. there were 1–3 cases of mesothelioma observed in the referent group, which may have attenuated the observed effects.

A high incidence of mesothelioma was reported among residents of Biancavilla, Italy, a city in eastern Sicily (SMR, 7.21; 95%CI: 3.59–13.00). Reviewing of the work histories of the cases did not indicate an occupational explanation for these exposures, and thus environmental explanations for the mesothelioma excess were sought. Environmental studies have indicated that these mesotheliomas are most likely due to exposures to fluoro-edenite which is a newly recognized fibre that is very similar in morphology and composition to the tremolite-actinolite series (Comba *et al.*, 2003; Bruno *et al.*, 2006; Putzu *et al.*, 2006).

2.4 Other cancer sites

Beyond lung cancer and mesothelioma, the body of literature examining associations between asbestos and other cancers is more sparse. This reflects the fact that lung cancer and mesothelioma have been the principal areas of research

until relatively recently, and other cancers were often not considered in detail in published reports. Clinical and epidemiological studies that span the past five decades suggest, however, that asbestos may be associated with other cancers in addition to lung cancer and mesothelioma. To examine these associations in detail, the US IOM (2006) published a report evaluating the evidence relevant to causation of cancer of the pharynx, larynx, oesophagus, stomach, colon and rectum by asbestos. The present analysis draws on the IOM analysis and presents the most significant positive and negative studies for each anatomical site, with an emphasis on studies that presented data on dose–response as well as on published meta-analyses. Additionally, the present analysis examines the association between asbestos exposure and ovarian cancer, an association that was not examined by the IOM.

2.4.1 Cancer of the pharynx

See Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.5.pdf.

(a) Cohort Studies

The Working Group examined 16 cohort studies of asbestos and cancer of the pharynx. Some of these studies examined all cancers of the lips, oral cavity, and pharynx. Others restricted their examination to the pharynx itself. Two studies examined only cancers of the hypopharynx. The main findings are summarized in the following paragraphs.

Selikoff & Seidman (1991) observed an SMR for cancer of the oropharynx of 2.18 (95%CI: 1.62–2.91) among a cohort of 17800 male asbestos insulation workers across the USA and Canada. This is the cohort study with the largest number of deaths from pharyngeal cancer, a total of 48 deaths.

Piolatto *et al.* (1990) observed an SMR for cancer of the oropharynx of 2.31 (95%CI: 0.85–5.02; based on six deaths) in a cohort of 1058 asbestos miners in northern Italy exposed to chrysotile asbestos. No association was seen in this cohort between duration of occupational exposure to asbestos and risk of cancer of the pharynx.

Reid *et al.* (2004) observed an SMR for cancer of the pharynx of 1.88 (95%CI: 1.15–3.07; based on 16 deaths) in a cohort of 5685 crocidolite asbestos miners and millers in Western Australia.

Sluis-Cremer *et al.* (1992) observed an SMR for cancer of the lip, oral cavity and pharynx of 2.14 (95%CI: 1.03–3.94; based on 10 deaths) in a cohort of 7317 male asbestos miners in South Africa, some exposed to crocidolite and others to amosite. Cancer of the pharynx was defined in this population as cancer of the lip, oral cavity or pharynx. There was no excess mortality for cancer of the pharynx in the subcohort of amosite asbestos miners (SMR, 0.42; 95%CI: 0.00–1.97), but in the subcohort of crocidolite asbestos miners, the SMR for cancer of the pharynx was 2.94 (95%CI: 1.16–6.18).

Pira *et al.* (2005) observed an SMR for cancer fo the pharynx of 2.26 (95%CI: 0.90–4.65; based on seven deaths) in a cohort of 1996 workers in the asbestos textiles industry in Italy.

Other cohort studies of populations occupationally exposed to asbestos in a range of industries contained only small numbers of deaths from cancer of the pharynx (most < 10 deaths), were generally non-positive in their findings, and reported little evidence for dose–response relationships.

(b) Case–control studies

Case–control studies examining the association between asbestos exposure and cancer of the pharynx have two advantages over cohort studies:

1. they are able to collect more cases of this relatively uncommon malignancy; and
2. they are able to adjust for alcohol and tobacco consumption, the two most common causes

of cancer of the pharynx in developed and developing countries.

The present review included six case–control studies. Four of them adjusted for alcohol and tobacco consumption. The main findings are summarized in the following paragraphs.

Marchand *et al.* (2000) carried out a hospital-based, case–control study of 206 cases of cancer of the hypopharynx and 305 controls in France, and found a relative risk of 1.80 (95%CI: 1.08–2.99) in the 161 of their cases ever exposed to asbestos, adjusted for exposure to tobacco and alcohol.

Berrino *et al.* (2003) conducted a multicentre, case–control study of cancer of the hypopharynx in Europe, and found an odds ratio (OR) for "probable" exposure to asbestos of 1.8 (95%CI: 0.6–5.0). This study was restricted to analyses of cancers of the hypopharynx. For cases with "possible" exposure to asbestos, the odds ratio was 1.80 (95%CI: 0.90–3.90). These odds ratios were adjusted for exposure to tobacco and alcohol.

Zheng *et al.* (1992) conducted a population-based, case–control study of cancer of the pharynx in Shanghai, the People's Republic of China, with 204 incident cancer cases and 414 controls. The relative risk for asbestos exposure was 1.81 (95%CI: 0.91–3.60). Cigarette smoking and alcohol consumption were observed to be positively associated with cancer fo the pharynx. By contrast, increasing intake of certain fruits and vegetables, notably oranges, tangerines and Chinese white radishes, appeared to be associated with a reduced risk for cancer of the pharynx.

(c) Meta-analyses

The IOM (2006) conducted a meta-analysis of the published cohort studies examining the association between asbestos exposure and cancer of the pharynx. The IOM noted that the findings of the cohort studies were consistently positive. They calculated that the "estimated aggregated relative risk of cancer of the pharynx from any exposure to asbestos was 1.44 (95%CI: 1.04–2.00). "The IOM noted that few studies had evaluated dose–response trends, and that there was no indication of higher risks associated with more extreme exposures."

The IOM also conducted a meta-analysis of the case–control studies examining the association between asbestos exposure and cancer of the pharynx. The IOM reported the summary relative risk for cancer of the pharynx in people with "any" exposure to asbestos compared to people with no exposure to be 1.5 (95%CI: 1.1–1.7). The IOM observed that the studies were inconsistent, and that there was little evidence for a dose–response relationship.

2.4.2 Cancer of the larynx

See Table 2.5 online.

Cancer of the larynx in relation to asbestos exposure has been studied in a large number of cohort and case–control studies undertaken among occupationally exposed populations in North and South America, Europe, and Asia. (IOM, 2006).

(a) Cohort studies

Cohort studies of workers exposed occupationally to asbestos have found evidence for an association between asbestos exposure and cancer of the larynx across a broad range of industries. The Working Group reviewed 29 cohort studies encompassing 35 populations exposed to asbestos. Noteworthy findings from among these studies are summarized in the following paragraphs.

Selikoff & Seidman (1991) found an SMR for cancer of the larynx of 1.70 (95%CI: 1.01–1.69) among 17800 male insulation workers in the USA and Canada.

Musk *et al.* (2008) found an SMR for cancer of the larynx of 1.56 (95%CI: 0.83–2.67) among 6943 asbestos miners and millers from Western Australia, exposed predominantly to crocidolite

asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last know to be alive, the SMR was 2.57 (95%CI: 1.37–4.39).

Reid *et al.* (2004) carried out a study of cancer incidence in this same Australian cohort, and found a significant increase in incidence of cancer of the larynx (SIR, 1.82; 95%CI: 1.16–2.85).

Piolatto *et al.* (1990) found an SMR for cancer of the larynx of 2.67 (95%CI: 1.15–5.25; based on eight deaths) in a cohort study of 1058 male asbestos miners in northern Italy. In the subset of this cohort with > 20 years' exposure to asbestos, the SMR for cancer of the larynx was 4.55 (95%CI: 1.47–10.61). There was evidence of a positive dose–response relationship between cumulative exposure to asbestos dust, measured as fibre–years, and risk of death from cancer of the larynx. The SMRs for cancer of the larynx were 1.43 (95%CI: 0.04–7.96) in workers with exposure < 100 fibre–years; 2.22 (95%CI: 0.27–8.02) in workers with exposure of 100–400 fibre–years; and 3.85 (95%CI: 1.25–8.98) in workers with cumulative exposure > 400 fibre–years.

Peto *et al.* (1985) found an overall SMR for cancer of the larynx of 1.55 (95%CI: 0.42–3.97; based on four deaths) in a cohort of 3211 asbestos-textile workers in the United Kingdom. When workers were subdivided according to time since first employment, and by duration of employment in "scheduled" (asbestos-exposed) areas of the plant, four deaths from cancer of the larynx were observed in the most heavily exposed group versus 1.53 expected (SMR, 2.55).

Pira *et al.* (2005) found an overall SMR for cancer of the larynx of 2.38 (95%CI: 0.95–4.90; based on seven deaths–all of them in male workers) in a cohort of 889 men and 1077 women employed in an asbestos textiles plant in Italy.

Raffn *et al.* (1989) found an overall SIR for cancer of the larynx of 1.66 (95%CI: 0.91–2.78) in a cohort study of 7986 men and 584 women employed in the asbestos-cement industry in Denmark However, in the subset with > 5 years employment, the SIR was 2.27 (95%CI: 0.83–4.95), and in the group first employed from 1928–40, the SIR was 5.50 (95%CI: 1.77–12.82).

(b) Case–control studies

Case–control studies are important in examining relationships between asbestos exposure and cancer of the larynx, because they overcome the relative rarity of the diagnosis in cohort studies, and also because they permit consideration of potential confounding by exposure to tobacco and alcohol, the two most important risk-factors for this malignancy in developed and developing countries.

The Working Group analysed 15 case–control studies of asbestos and cancer of the larynx. This analysis revealed that 14 of the 15 published studies had found evidence for a significantly positive association between asbestos exposure and cancer of the larynx; only one study (Luce *et al.*, 2000) reported an odds ratio below 1.0.

(c) Meta-analyses

The IOM conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the larynx. For studies examining "any" versus no exposure, the summary relative risk was 1.4 (95%CI: 1.19–1.64). For studies comparing "high" exposure versus no exposure, the lower bound summary relative risk was 2.02 (95%CI: 1.64–2.47), and the upper bound summary relative risk was 2.57 (95%CI: 1.47–4.49).

The IOM also conducted a meta-analysis of the published case–control studies examining the association between asbestos exposure and cancer of the larynx (IOM, 2006). This meta-analysis calculated a summary relative risk of 1.43 (95%CI: 1.15–1.78), before adjusting for consumption of tobacco and alcohol. After adjusting for tobacco and alcohol consumption, the association of cancer of the larynx with

asbestos exposure persisted, with an adjusted summary relative risk of 1.18 (95%CI: 1.01–1.37).

2.4.3 Cancer of the oesophagus

See Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.6.pdf.

(a) Cohort studies

The Working Group examined 25 studies of cohorts occupationally exposed to asbestos. Notable findings from among these studies are:

Selikoff & Seidman (1991) found an SMR for cancer of the oesophagus of 1.61 (95%CI: 1.13–2.40) among a cohort of 17800 asbestos insulations workers across the USA and Canada. Selikoff & Seidman (1991) observed that cancer in asbestos workers is "very much related to latency," with most of the increased risk occurring only 25 or more years from the onset of occupational exposure to asbestos.

In a cohort of 10939 male and 440 female asbestos miners and millers in Quebec, Canada, exposed predominantly to chrysotile asbestos, followed through 1975, McDonald *et al.* (1980) reported that mortality for cancer of the oesophagus and stomach (the two were combined) was elevated (SMR, 1.27). Further follow-up through 1988 of a subset of this cohort, consisting of 5335 men, examined esophageal cancer mortality separate from stomach cance,r and found no excess mortality (SMR, 0.73; 95%CI: 0.35 – 1.34) (McDonald *et al.*, 1993).

Musk *et al.* (2008) found an SMR for cancer of the oesophagus was 1.01 (95%CI: 0.71–1.40) in a cohort study of 6943 asbestos miners from Western Australia followed through 2000, exposed predominantly to crocidolite asbestos, when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring all subjects at the date last known to be alive, the SMR was 1.20 (95%CI: 0.62–2.10).

Hein *et al.* (2007) found an SMR for cancer of the oesophagus of 1.87 (95%CI: 1.09–2.99) in a cohort of 3072 asbestos textile workers in South Carolina, occupationally exposed to chrysotile asbestos and followed through 2001.

Peto *et al.* (1985) found 11 deaths from cancer of the oesophagus versus 6.59 expected (SMR = 1.67; 95%CI: 0.83–2.99) in a cohort of 3211 male asbestos textile workers in the United Kingdom. For the subset of workers with 10+ years employment in "scheduled" (asbestos-exposed) areas of the plant and with 20+ years since first employment, the SMR for cancer of the oesophagus was 2.36 (95%CI: 0.49–6.91). For all workers in this cohort with < 20 years since first employment, two deaths for cancer of the oesophagus was observed versus 2.18 expected, and for workers with 20+ years since first employment, there were nine deaths from cancer of the oesophagus versus 4.4 expected (see Table 6 in Peto *et al.*, 1985).

Berry *et al.* (2000) found a 2-fold excess mortality for cancer of the oesophagus (SMR, 2.08; 95%CI: 1.07–3.63) among a cohort of over 5000 asbestos-exposed factory workers in the east end of London, United Kingdom, who had produced asbestos insulation boards, and who were followed for 30+ years. In the subset of workers within this population with "severe" asbestos exposure of more than 2 years' duration, the SMR for cancer of the oesophagus was 5.62 (95%CI: 1.82 – 13.11). And in the subset of women with "severe" exposure to asbestos of > 2 years, the SMR for cancer of the oesophagus was 9.09 (95%CI: 1.10–32.82).

Other cohort studies of various groups occupationally exposed to asbestos – asbestos-cement workers, friction products workers, and "generic" asbestos workers – yield generally non-positive results for cancer of the oesophagus.

(b) Case–control studies

The Working Group examined five case–control studies that examined the association between asbestos exposure and cancer of the oesophagus.

A case–control study in Quebec, Canada found an OR of 2.0 (95%CI: 1.1–3.8) for any exposure to asbestos among 17 patients diagnosed with squamous cell carcinoma of the oesophagus. (Parent *et al.*, 2000).

A case–control study conducted within a cohort of nearly 400000 Swedish construction workers found evidence for a positive association between asbestos exposure and adenocarcinoma of the oesophagus. Relative risk increased from 1.0 (reference) among workers with no asbestos exposure, to 1.7 (95%CI: 0.5–5.4) among those with "moderate" exposure, and to 4.5 (95%CI: 1.4–14.3) among those workers with "high" asbestos exposure, thus suggesting a positive dose–response relationship (Jansson *et al.*, 2005).

(c) Meta-analyses

Meta-analyses have been undertaken of the association between asbestos exposure and cancer of the oesophagus:

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to the percentage of deaths due to mesothelioma. The rationale is that a higher death rate for either lung cancer or mesothelioma is taken to be a surrogate index of higher cumulative exposure to asbestos. However, no association was observed between death rate for cancer of the oesophagus in the published cohorts by either lung cancer SMR or percentage of death for mesothelioma.

Meta-analyses by Edelman (1988) and by Goodman *et al.* (1999) did not detect an association between asbestos exposure and cancer of the oesophagus.

A meta-analysis by Morgan *et al.* (1985) that examined earlier studies, which tended to have heavier exposure, found a summary SMR for cancer of the oesophagus in asbestos-exposed workers of 2.14 (95%CI: 1.326–3.276). When cases of cancer of the oesophagus based on "best evidence" (pathological review) were deleted from these cohorts, the SMR remained elevated at 2.38 (95%CI: 1.45–3.68).

The IOM (2006) conducted a meta analysis of 25 cohort studies and reported a summary relative risk of 0.99 (95%CI: 0.78–1.27) for any exposure to asbestos versus no exposure. The IOM also examined the relative risk of "high" versus no exposure, and calculated a lower bound summary relative risk of 1.35 (95%CI: 0.81–2.27), and a higher bound summary relative risk of 1.43 (95%CI: 0.79–2.58). The IOM determined that there were too few case–control studies to permit a meta-analysis.

2.4.4 Cancer of the stomach

The Working Group reviewed 42 cohort studies and five population-based case–control studies that examined the association between asbestos and cancer of the stomach (See Table 2.6 online).

(a) Cohort studies

Notable findings among the cohort studies are:

Selikoff *et al.* (1964) reported a nearly 3-fold excess mortality for cancer of the stomach (12 observed versus 4.3 expected) in a population of 632 insulation workers in New York and New Jersey occupationally exposed to asbestos dust. Further analysis within this cohort (Selikoff *et al.*, 1979) found evidence of a dose–response relationship between duration of exposure to asbestos (in years), and risk of death from cancer of the stomach. The SMR for cancer of the stomach increased from 0.00 in workers exposed for < 20 years, to 4.00 (95%CI: 1.47 – 8.71) in those exposed for 20 –35 years, and to 3.42 (95%CI: 1.82 – 5.85) in those exposed for > 35 years.

Selikoff *et al.* (1967) found a modest, non-significant increase in risk of death for cancer of the stomach: 34 observed v. 29.4 expected, (SMR = 1.16;95%CI: 0.92 – 1.78) in a larger cohort study of 17800 insulation workers across the USA and Canada. No data on dose–response for cancer of the stomach were presented in this analysis.

Liddell *et al.* (1997) reported an overall SMR for cancer of the stomach of 1.24 (95%CI: 1.07 –1.48) in a study of 10918 asbestos miners and millers exposed predominantly to chrysotile asbestos, in Quebec, Canada. Within this cohort, a positive dose–response relationship was observed between cumulative exposure to asbestos dust (mcpf-year) and mortality for cancer of the stomach. Thus, for workers with cumulative dust exposure < 300, the SMR was 1.16; for workers with cumulative exposure of 300 – 400, the SMR was 1.29; for workers with cumulative exposure of 400 – 1000, the SMR was 1.21; and for workers in the highest exposure category, with cumulative exposure > 1000, the SMR was 3.21 (95%CI: 1.87 –5.14). An additional finding in this cohort was a modest interaction between cumulative asbestos exposure, cigarette smoking, and mortality from cancer of the stomach.

Musk *et al.* (2008) found an SMR for cancer of the stomach of 1.01 (95%CI: 0.71 – 1.40) in a cohort of 6943 asbestos miners and millers exposed predominantly to crocidolite asbestos in Wittenoom, Western Australia, followed through the end of 2000, and when all cohort members lost to follow-up were assumed to be alive. When the analysis was re-run censoring subjects at the date last known to be alive, the SMR was 1.71 (95%CI: 1.20–2.35).

Reid *et al.* (2004) conducted a nested case–control study within this same Australian cohort, and found a positive exposure-response relationship between cancer of the stomach and cumulative exposure to asbestos (test for trend, P = 0.057). No association was seen between cancer of the stomach and either time since first exposure or year of starting work with asbestos. Smoking status was associated with cancer of the stomach, but not significantly.

Meurman *et al.* (1974) found a non-significant increase in SMR for cancer of the stomach: SMR = 1.42 (95%CI: 0.76 – 2.43) in a cohort of 736 asbestos miners in Finland exposed to anthophyllite asbestos.

Berry *et al.* (2000) found a modest, non-significant increased risk for death from cancer of the stomach: 28 observed versus 23.1 expected (SMR, 1.21; 95%CI: 0.81–1.75) in a British study of factory workers producing asbestos insulation in the east end of London.

Strongly positive dose–response associations between cumulative asbestos response and cancer of the stomach were observed in two cohort studies of Chinese factory workers – one in Beijing and the other in Qingdao; relative risks for cancer of the stomach were 4.4 and 2.4, respectively (Zhu & Wang, 1993; Pang *et al.*, 1997).

Raffn *et al.* (1989) observed 43 deaths from cancer of the stomach versus 30.09 expected (SMR, 1.43; 95%CI: 1.03 – 1.93) in a cohort of 7986 men employed from 1928–84 in the asbestos cement industry in Denmark.

Enterline *et al.* (1987) observed a SMR for cancer of the stomach of 1.80 (95%CI: 1.10–2.78) in a cohort of 1074 retired US asbestos workers.

Epidemiological studies of cohorts with asbestos-related diseases – asbestosis and benign pleural disease – have not found increased mortality for cancer of the stomach (Germani *et al.*, 1999; Karjalainen *et al.*, 1999; Szeszenia-Dabrowska *et al.*, 2002).

(b) Case–control studies

Case–control studies exploring the relationship between asbestos exposure and cancer of the stomach yield inconsistent results. The Working Group reviewed five case–control studies. Notable findings are these:

A study from Poland (Krstev *et al.*, 2005) found an OR for cancer of the stomach of 1.5 (95%CI: 0.9–2.4) for workers ever exposed to asbestos, and of 1.2 (95%CI: 0.6–2.3) for workers with 10 or more years of exposure to asbestos.

The largest case–control study to examine the association between asbestos and cancer of the stomach (Cocco *et al.*, 1994) reported an odds ratio of 0.7 (95%CI: 0.5–1.1) for workers ever exposed to asbestos, and of 1.4 (95%CI: 0.6–3.0) for those with 21+ years of exposure to asbestos.

The most strongly positive case–control study linking asbestos to cancer of the stomach is the case–control study, cited above, nested within the Western Australia mining cohort (Reid *et al.*, 2004).

(c) Meta-analyses

Several meta-analyses have been undertaken of the association between asbestos exposure and cancer of the stomach.

A meta-analysis by Frumkin & Berlin (1988) stratified studies according to SMR for lung cancer and also according to percentage of deaths due to mesothelioma. Frumkin & Berlin found in cohorts where the SMR for lung cancer was < 2.00 that the SMR for cancer of the stomach was 0.91 (95%CI: 0.71–1.16). By contrast, when the SMR for lung cancer was > 2.00, the SMR for cancer of the stomach increased to 1.34 (95%CI: 1.07–1.67).

Gamble (2008) reported that point estimates for cancer of the stomach mortality tended towards 1.0 when the excess risk for lung cancer were less than 4-fold, but "tended to be somewhat elevated when lung cancer relative risks were 4-fold or greater." Gamble observed further that "combined relative risks for cancer of the stomach stratified by lung cancer categories showed a suggestive trend, with a significant deficit (0.80) when lung cancer SMRs were <1.0 that increased monotonically to a significant 1.43-fold excess in the studies with lung cancer SMRs > 3.0." Gamble observed no trend for increasing SMR for cancer of the stomach with increasing percentage of deaths from mesothelioma (Gamble, 2008).

The IOM (2006) conducted a meta-analysis of 42 cohort studies examining the association between asbestos exposure and cancer of the stomach. The IOM noted that the "majority of cohort relative risk estimates for cancer of the stomach exceed the null value (1.0), indicating excesses, although estimates varied considerably in strength." In cohorts that compared "any" versus no exposure, the summary relative risk was 1.17 (95%CI: 1.07–1.28). The IOM notes that with respect to dose–response, the summary estimates were stable. Thus in the cohorts that compared "high" versus no exposure, the lower bound summary relative risk was 1.31 (95%CI: 0.97–1.76), and the higher bound summary relative risk, 1.33 (95%CI: 0.98–1.79).

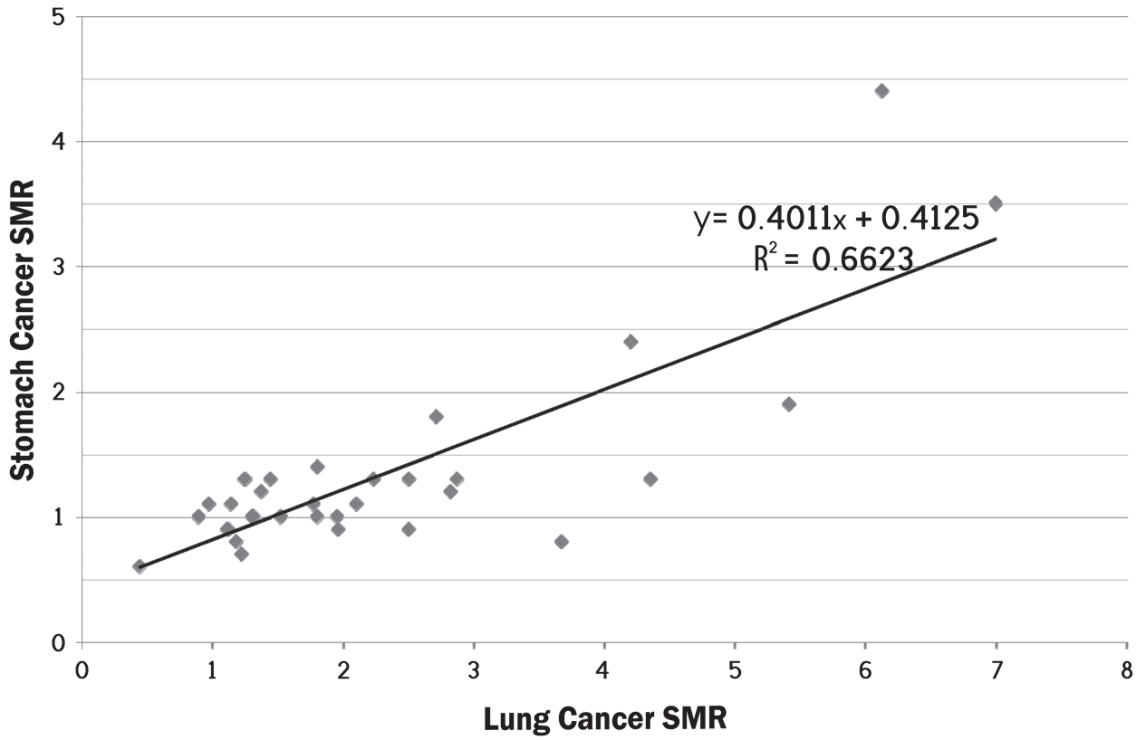
The IOM conducted a meta-analysis of the five case–control studies resulting in a combined relative risk of 1.11 (95%CI: 0.76–1.64). The summary odds ratio increased when only extreme exposure was considered (OR, 1.42; 95%CI: 0.92–2.20)

The Working Group developed a scatter plot comparing SMRs for lung cancer with SMRs for cancer of the stomach in the same cohorts. A positive trend was observed between the two, and the correlation coefficient (r2) = 0.66, see Fig. 2.1.

(i) Asbestos in drinking-water and cancer of the stomach

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the stomach. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Levy *et al.* (1976) reported an excess in cancer of the stomach among persons in Duluth, MN, USA exposed to taconite asbestos in drinking-water. Wigle (1977) saw an excess of male cancer of the stomach among some exposed to asbestos in drinking-water in Quebec. Conforti *et al.* (1981)

Fig 2.1 Stomach & lung cancer correlation in asbestos cohorts



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saw a similar association in the San Francisco Bay area, USA. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. They observed no association between asbestos exposure and cancer of the stomach. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined cancer of the stomach incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. They found an SIR for cancer of the stomach in the entire cohort of 1.6 (95%CI: 1.0–2.3). In the subcohort with "definite" exposure to asbestos, the SIR was 2.5 (95%CI: 0.9–5.5). In those members of the definite exposure subcohort followed for 20+ years, the SIR was 1.7 (95%CI: 1.1–2.7).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and cancer of the stomach, and concluded that the available data were inadequate to evaluate the cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada, and found no consistent pattern of association.

2.4.5 Cancer of the colorectum

The Working Group examined data from 41 occupational cohorts and 13 case–control studies that reported data on associations between asbestos exposure and cancer of the colon and rectum (See Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.7.pdf). The Working Group made the decision to combine information on these two sites, although a few comments in several places in the text about the two sites considered separately have also been made.

(a) Cohort studies

An association between occupational exposure to asbestos and cancer of the colorectum was first reported in 1964 by Selikoff *et al.* in a cohort of 632 male insulation workers in New York and New Jersey, USA (Selikoff *et al.*, 1964). Further analysis of this cohort found a positive relationship between duration of work with asbestos and risk of cancer of the colorectum, in that the SMR increased from 0.00 (95%CI: 0.00–18.45) in workers with < 20 years exposure, to 3.68 (95%CI: 1.48–7.59) among workers with 20–35 years' exposure, and to 2.58 (95%CI: 1.48–4.19) among workers with the longest duration of exposure, > 35 years (Selikoff & Hammond, 1979).

Selikoff *et al.* (1967), in a second report, found an association between occupational exposure to asbestos and cancer of the colorectum in a population of 17800 asbestos insulators across the USA and Canada (SMR, 1.37; 95%CI: 1.14–1.64).

Seidman *et al.* (1986) reported an elevated mortality from cancer of the colorectum in a population of 820 male factory workers in Paterson, NJ, USA, exposed to amosite asbestos (SMR, 2.77; 95%CI: 1.16–2.80). They noted that cancer of the colorectum in asbestos workers tended to be a disease of long latency; they reported that the ratio of observed to expected deaths increased with increasing interval since initial exposure to asbestos.

McDonald *et al.* (1980) reported an overall SMR for cancer of the colorectum of only 0.78 in a study of 10939 men and 440 women workers employed as asbestos miners and millers in Quebec with predominant exposure to chrysotile asbestos. Additionally, however, McDonald *et al.* reported a "clear trend for SMRs to be higher, the heavier the exposure." Thus with increasing levels of cumulative occupational exposure to asbestos dust, relative risks for cancer of the colorectum increased in this cohort from 1.00 in workers with less than 30 mpcf–y cumulative exposure, to 0.93 in workers with 30–300 mpcf–y, to 1.96 in workers with 300–1000 mpcf–y, and then in the group with heaviest exposure, > 1000 mpcf–y, to 5.26.

Albin *et al.* (1990) found an overall SMR for cancer of the colorectum of only 1.5 (95%CI: 0.7–3.0) in a cohort of 1465 asbestos-cement workers in Sweden. A positive association between asbestos exposure and cancer of the colorectum was reported, but when cancer of the colorectum mortality was examined by individual cumulative exposure to asbestos, measured as fibre–years/mL, the SMR was 1.3 (95%CI: 0.5–2.9) for those workers with cumulative exposure of < 15 fibre–years/mL; for those with cumulative exposure of 15–39 fibre–years/mL, the SMR was 1.1(95%CI: 0.3–3.9); and for those workers in highest exposure category with > 40 fibre–years/mL, the SMR for cancer of the colorectum was 3.4 (95%CI: 1.2–9.5). Diagnosis in all but one of the cancers in the highest exposure category was verified by pathological review, and no case of certified or probable mesothelioma was found. The trend towards increasing mortality from cancer of the colorectum with increasing cumulative exposure to asbestos was statistically significant ($P = 0.04$). A similar trend was seen for cancer of the colorectum morbidity.

Excess mortality from colon cancer was observed in a heavily exposed cohort of over

5000 workers in the east end of London, who had produced asbestos insulation board and were followed for 30+ years (Berry *et al.*, 2000). The overall SMR for colon cancer in this cohort was 1.83 (95%CI: 1.20–2.66). There was evidence for a positive dose–response relationship, in that excess mortality from colon cancer was confined to men who had worked as laggers or had been severely exposed for more than 2 years. This positive trend was statistically significant ($P = 0.017$).

In a cohort comprised of family members of men who had been employed in an asbestos-cement factory in Casale Monferrato, Italy, Ferrante *et al.* (2007) examined cancer mortality. Among women with domestic exposure to asbestos, 21 deaths from cancer of the "intestine and rectum" versus 16.0 expected (SMR, 1.31; 95%CI: 0.81–2.0) were observed. For cancer of the rectum, ten deaths versus five expected (SMR, 2.00; 95%CI: 0.96–3.69) were observed.

Several other cohort studies of occupationally exposed populations in a variety of industries have also found evidence for an association between asbestos exposure and cancer of the colorectum (Puntoni *et al.*, 1979: Hilt *et al.*, 1985; Jakobsson *et al.*, 1994; Raffn *et al.*, 1996; Szeszenia-Dabrowska *et al.*, 1998; Smailyte *et al.*, 2004).

Jakobsson *et al.* (1994) examined colon cancer by anatomical location in asbestos-cement workers, and observed an increased incidence of malignancy in the right side of the colon, but not in the left side.

A report on incidence of cancer of the colorectum from the Beta-Carotene and Retinol Efficacy Trial (CARET) found a relative risk of 1.36 (95%CI: 0.96–1.93) among 3987 heavy smoker participants occupationally exposed to asbestos as compared to smoker participants not exposed to asbestos (Aliyu *et al.*, 2005). Of note was the finding that the relative risk for cancer of the colorectum was 1.54 (95%CI: 0.99–2.40) among participants with asbestos-induced pleural plaques. The investigators interpreted the presence of pleural plaques as a marker for heavy individual exposure to asbestos. Risk for cancer of the colorectum also increased with worsening pulmonary asbestosis ($P = 0.03$ for trend). It was reported that a "dose–response trend based on years of asbestos exposure was less evident".

(b) *Case–control studies*

Evidence from case–control studies of asbestos and cancer of the colorectum is in general less strong than the evidence from the cohort studies. However, case–control studies from the Nordic countries and the USA have, however, reported significant increases in asbestos-associated odds ratios in occupationally exposed poulations (Fredriksson *et al.*, 1989; Gerhardsson de Verdier *et al.*, 1992; Vineis *et al.*, 1993; Kang *et al.*, 1997; Goldberg *et al.*, 2001).

Consideration of latency since first exposure appears to be an important factor in assessing these studies. Thus, Gerhardsson de Verdier *et al.* (1992) examined incidence of cancer of the colorectum by interval since first occupational exposure and observed "for subjects exposed to asbestos, the risks were highest when the latency period was more than 39 years." Gerhardsson de Verdier *et al.* observed further that the relative risk for cancer of the right colon was 2.6 (95%CI: 1.2–5.9) among workers exposed to asbestos, and that for malignancy of the left colon, only 0.5 (95%CI: 0.1–1.9).

Other cohort and case–control studies have not found evidence for an association between asbestos exposure and cancer of the colorectum (Gardner *et al.*, 1986; Hodgson & Jones, 1986; Garabrant *et al.*, 1992; Dement *et al.*, 1994; Demers *et al.*, 1994; Tulchinsky *et al.*, 1999; Hein *et al.*, 2007; Loomis *et al.*, 2009).

(c) *Meta-analyses*

Some of these meta-analyses have stratified studies according to the standardized mortality ratio for lung cancer or the percentage of deaths due to mesothelioma:

Morgan *et al.* (1985) found a summary standardized mortality ratio for cancer of the colorectum of 1.13 (95%CI: 0.97–1.30). This was reduced to 1.03 (95%CI: 0.88–1.21) after deleting cases in which the diagnosis of cancer of the colorectum was based on "best evidence" (pathological review) rather than death certificate data.

Frumkin & Berlin (1988) found in cohorts where the standardized mortality ratio for lung cancer was < 2.00 that the standardized mortality ratio for cancer of the colorectum was 0.86 (95%CI: 0.69–1.09). By contrast, when the standardized mortality ratio for lung cancer was > 2.00, the standardized mortality ratio for cancer of the colorectum increased to 1.61 (95%CI: 1.34–1.93).

Homa *et al.* (1994) found an elevated summary standardized mortality ratio for cancer of the colorectum in cohorts exposed to serpentine asbestos that had an standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.73; 95%CI: 0.83–3.63), and also in cohorts exposed to a mix of amphibole and serpentine asbestos that had a standardized mortality ratio for lung cancer > 2.00 (summary standardized mortality ratio for cancer of the colorectum, 1.48; 95%CI: 1.24–1.78). Among cohorts exposed to amphibole asbestos, the standardized mortality ratio for cancer of the colorectum was elevated regardless of the standardized mortality ratio for lung cancer. Homa *et al.* (1994) saw similar trends between standardized mortality ratio for cancer of the colorectum and percentage of deaths from mesothelioma.

Gamble (2008) reported that there was "tendency for CRC [cancer of the colorectum] risk ratios to be elevated when lung cancer risk ratios are >4" and further noted a significantly elevated standardized mortality ratio of 1.60 (95%CI: 1.29–2.00) for cancer of the colorectum when the standardized mortality ratio for lung cancer exceeds 3.00. Gamble (2008) observed no trend in cancer of the colorectum mortality with increasing percentage of deaths due to mesothelioma. Gamble saw no association between asbestos exposure and rectal cancer.

The IOM (2006) conducted a meta-analysis of cohort studies examining the association between asbestos exposure and cancer of the colorectum. In studies that compared "any" versus no exposure, the summary relative risk was 1.15 (95%CI: 1.01–1.31). For studies comparing "high" versus no exposure, the lower-bound summary relative risk was 1.24 (95%CI: 0.91–1.69), and the upper-bound summary relative risk, 1.38 (95%CI: 1.14–1.67).

The IOM also conducted a meta-analysis of the published case–control studies. Overall, 13 studies comparing "any" versus no exposure yielded a summary relative risk of 1.16 (95%CI: 0.90–1.49).

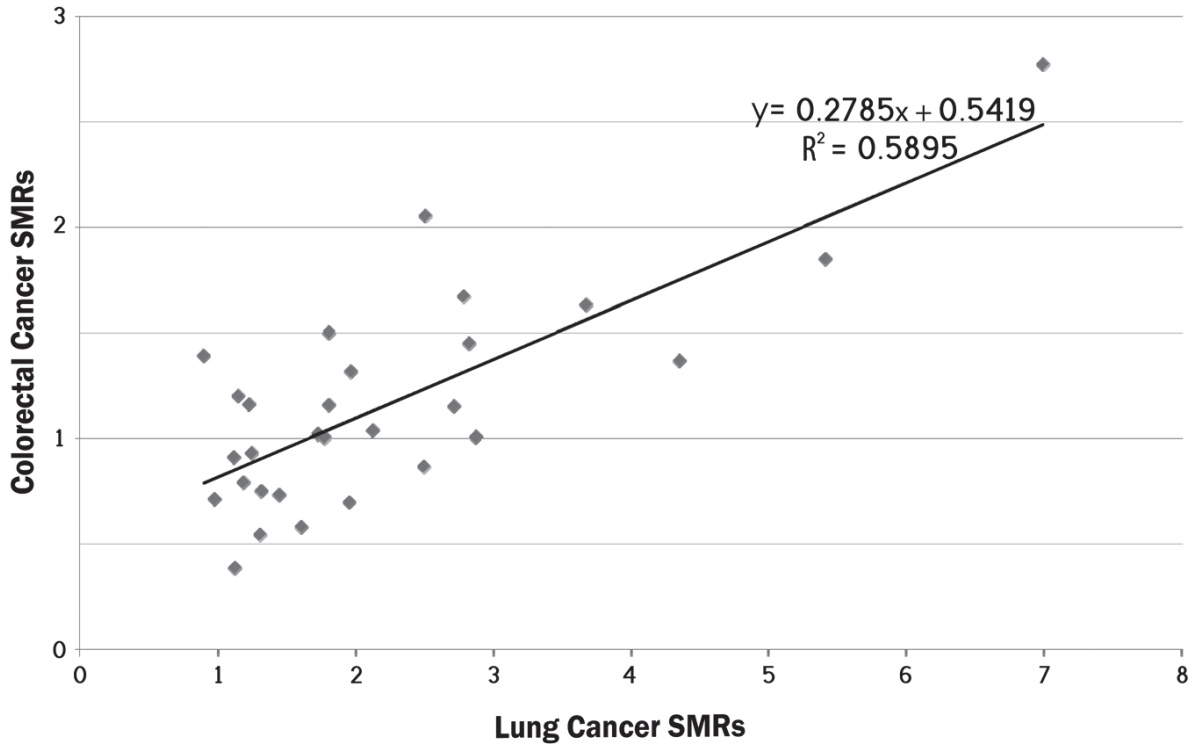
The *IARC Monograph* 100C Working Group developed a scatter plot comparing standardized mortality ratios for lung cancer with standardized mortality ratios for cancer of the colorectum in the same cohorts. The trend was positive with a correlation coefficient (r2) of 0.59, see Fig. 2.2.

(i) Asbestos in drinking-water and cancer of the colorectum

Ecological correlational studies conducted from the 1960s into the early 1980s suggested an association between asbestos in drinking-water and cancer of the colon. These studies correlated population exposure to asbestos in water supplies with population cancer rates. Polissar *et al.* (1982) examined cancer incidence and mortality among residents of the Puget Sound area, USA, in relation to asbestos in regional drinking-water. No association between asbestos exposure and colon cancer was observed. A similarly negative study was observed in a study conducted in Woodstock, NY, USA (Howe *et al.*, 1989).

Kjærheim *et al.* (2005) examined colon cancer incidence in Norwegian light-house keepers exposed to asbestos in drinking-water. The standardized incidence ratio for colon cancer in

Fig 2.2 Colorectal & lung cancer correlation in asbestos cohorts



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the entire cohort was 1.5 (95%CI: 0.9–2.2). In the subcohort with "definite" exposure to asbestos, the standardized incidence ratio was 0.8 (95%CI: 0.1–2.9). In those members of the definite exposure subcohort followed for 20+ years, the standardized incidence ratio was 1.6 (95%CI: 1.0–2.5).

Cantor (1997) conducted a systematic review of the epidemiological literature on exposure to asbestos in drinking-water and colon cancer and concluded that the data were inadequate to evaluate colon cancer risk of asbestos in drinking-water.

Marsh (1983) conducted a critical analysis of 13 epidemiological studies of asbestos and drinking-water conducted in the USA and Canada and found no consistent pattern of association.

2.4.6 Cancer of the ovary

The published literature examining the association between asbestos exposure and cancer of the ovaries is relatively sparse, because the workforce occupationally exposed to asbestos in such occupations as mining, milling shipyard work, construction and asbestos insulation work has been predominantly male. An examination of the association between asbestos and ovarian cancer was not undertaken by the IOM (2006).

See Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-06-Table2.8.pdf.

(a) Cohort studies

The Working Group examined 11 cohort studies that examined the association between asbestos exposure and ovarian cancer in 13 populations, ten with occupational exposure to asbestos and three with community-based or residential exposure.

Acheson *et al.* (1982) examined a cohort in the United Kingdom consisting of two groups of women in separate factories (n = 1327), employed in the manufacture of asbestos-containing gas masks before and during World War II. One factory had used crocidolite asbestos, and the other had used chrysotile. Among 757 women in the plant that used crocidolite, 12 deaths from ovarian cancer were observed versus. 4.4 expected (SMR, 2.75; 95%CI: 1.42–4.81). Among 570 women in the plant that used chrysotile asbestos, five deaths were observed for ovarian cancer versus 3.4 expected (SMR, 1.48; 95%CI: 0.48–3.44).

Wignall & Fox (1982) conducted a 30-year, follow-up mortality study of a population of 500 women in the United Kingdom employed in the manufacture of asbestos-containing gas masks before and during World War II. The type of asbestos used was crocidolite. A total of six deaths from ovarian cancer were obserevd versus. 2.8 expected (SMR, 2.13). When the cohort was subdivided according to degree of exposure to asbestos, the highest mortality from ovarian cancer was found among the subgroup definitely exposed to asbestos from the early 1940s (SMR, 14.81; $P < 0.01$). Overall five deaths from ovarian cancer were found among women definitely exposed to asbestos (versus 0.63 expected), whereas none were found among women definitely not exposed to asbestos (versus 0.40 expected).

To address potential misclassification of some deaths in this cohort recorded on death certificates as ovarian cancer as opposed to peritoneal mesothelioma, Wignall & Fox (1982) conducted a histopathological review of the cases cases of diagnosed ovarian cancer for which tissue material was available. One of these three cases was found to be peritoneal mesothelioma, while the diagnosis of ovarian cancer was sustained in the other two cases.

In a cohort study of 700 women factory workers employed in an asbestos-board insulation manufacturing company in the east end of London and followed for 30+ years, Berry *et al.* (2000) observed nine deaths from ovarian cancer versus 3.56 expected (SMR, 2.53; 95%CI: 1.16–4.80) (Berry *et al.*, 2000), with evidence for a positive exposure–response relationship. Among women with low-to-moderate exposure to asbestos, two deaths were observed versus 0.54 expected; in the subset with "severe" asbestos exposure of < 2 years' duration, two deaths were observed versus 2.12 expected. (SMR, 0.94); and among women with severe exposure of > 2 years' duration, five deaths from ovarian cancer were observed versus 0.90 expected (SMR, 5.35).

An assessment was performed of the significance of the positive exposure–response trend (P = 0.18). To address the potential misclassification of some deaths in this cohort having been recorded as ovarian cancer as opposed to peritoneal mesothelioma, Newhouse *et al.* (1972) conducted a histopathological review of the four deaths that by 1972 had been recorded as due to ovarian cancer; three of the four had occurred in women with severe and prolonged exposure to asbestos. Histological material was available for two of these cases. In both, the diagnosis of ovarian cancer was confirmed.

Reid *et al.* (2008) reported on cancer mortality in a cohort of 2552 women and girls who lived in the crocidolite asbestos mining town of Wittenoom in Western Australia during 1943–92, who were not involved in asbestos

mining and milling. Environmental contamination of the town with asbestos dust is reported to have been extensive. The women's exposure was environmental and not occupational. There were nine deaths from ovarian cancer in this cohort (SMR, 1.26; 95%CI: 0.58–2.40).

Reid *et al.* (2009) conducted a cancer incidence study in the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos. Additionally, they examined cancer incidence in 416 women who had worked in various capacities in the Wittenoom crocidolite asbestos mines and mills. Among community residents, ten incident cases of ovarian cancer were observed (SIR, 1.18; 95%CI: 0.45–1.91). Among women workers employed in the asbestos factory, one case of ovarian cancer was observed (SIR, 0.49; 95%CI: 0.01–2.74).

To address the possibility that some diagnosed cases of ovarian cancer in this cohort might in fact have been cases of peritoneal mesothelioma, Reid *et al.* (2009) examined pathological material from nine of their cases. The diagnosis of ovarian cancer was sustained in every case.

Pira *et al.* (2005) conducted a cohort study of 1077 women employed for at least one month during 1946–84 in an asbestos-textile factory in Italy, and followed up to 1996. A variety of types of asbestos were used in the factory, including crocidolite. A non-significantly increased standardized mortality ratio of 2.61 was observed for cancer of the ovary, based on five deaths. Among women in this cohort with ≥ 10 years of employment with asbestos, the standardized mortality ratio for ovarian cancer was 5.73, based on three deaths. Among women with ≥ 35 years since first employment, the standardized mortality ratio for ovarian cancer was 5.37, based on two deaths. This cohort was heavily exposed to asbestos, as supported by a standardized mortality ratio for lung cancer among women of 5.95, and by the occurrence of 19 deaths from mesothelioma (12%) among 168 total deaths in women.

Magnani *et al.* (2008) examined cancer mortality among a cohort of former workers at a now closed asbestos-cement factory in Casale Monferrato, Italy. A mix of crocidolite and chrysotile asbestos was used in this factory. Among women workers, there was an excess of ovarian cancers: nine observed versus 4.0 expected (SMR, 2.27; $P < 0.05$). Among women workers with 30 or more years exposure, the standardized mortality ratio for ovarian cancer was 2.97. Bertolotti *et al.* (2008) described the same findings in the same cohort [in Italian].

Ferrante *et al.* (2007) examined cancer mortality in a cohort consisting of family members of men who had been employed in the asbestos-cement factory in Casale Monferrato, Italy, described in the preceding paragraph. Exposure was to a mix of crocidolite and chrysotile. Among women with domestic exposure to asbestos, 11 deaths from ovarian cancer were observed versus 7.7 expected (SMR, 1.42; 95%CI: 0.71–2.54).

Germani *et al.* (1999) examined mortality from ovarian cancer in a cohort of 631 women workers in Italy who had been compensated for asbestosis. The type of fibre to which the women were exposed was not specified. In the total cohort, there were nine deaths from ovarian cancer (SMR, 4.77; 95%CI: 2.18–9.06). In the subset of women from the asbestos-textile industry, there were four deaths from ovarian cancer (SMR, 5.26; 95%CI: 1.43–13.47). In the subcohort from the asbestos cement industry, there were five deaths from ovarian cancer (SMR = 5.40; 95%CI: 1.75 – 12.61).

Rösler *et al.* (1994) examined cancer mortality in a cohort of 616 women workers in Germany who had been occupationally exposed to asbestos. Proportionate mortality was computed according to cause of death. A total of 95% of the asbestos used in Germany at this time was chrysotile, but the authors state that "admixture of crocidolite cannot be excluded, particularly in the manufacture of asbestos textile." Two deaths

from ovarian cancer were observed versus 1.8 expected (SMR, 1.09; 95%CI: 0.13–3.95).

(i) Population-based cohort studies

Vasama-Neuvonen *et al.* (1999) conducted a case–control study of ovarian cancer of occupational exposures in Finland. The asbestos fibre type was not specified and the standardized incidence ratio was 1.30 (95%CI: 0.9–1.80) between ovarian cancer and exposure to "high levels of asbestos."

Pukkala *et al.* (2009) examined the incidence of ovarian cancer among women employed in various occupational categories in Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). Among the groups examined were plumbers, a group with known occupational exposure to asbestos. Fibre type was not specified. A total of four ovarian cancers were observed in these women plumbers. The standardized incidence ratio was 3.33 (95%CI: 0.91–8.52)

(b) Case–control studies

Langseth & Kjærheim (2004) conducted a nested case–control study to examine the association between asbestos exposure and ovarian cancer within a cohort of female pulp and paper workers in Norway that had previously been found to have excess mortality from ovarian cancer (37 ovarian cancers observed versus 24 expected; SIR, 1.50; 95%CI: 1.07–2.09). The asbestos fibre type was not specified. In the case–control study, the odds ratio for occupational exposure to asbestos, based on 46 cases of ovarian cancer, was 2.02 (95%CI: 0.72–5.66).

2.5 Synthesis

The Working Group noted that a causal association between exposure to asbestos and cancer of the larynx was clearly established, based on the fairly consistent findings of both the occupational cohort studies as well as the case-controlcase–control studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and laryngeal cancer-cancer of the larynx reported in several of the well-conducted cohort studies. This conclusion was further supported by the meta-analyses of 29 cohort studies encompassing 35 populations and of 15 case-controlcase–control studies of asbestos exposure and laryngeal cancercancer of the larynx undertaken by the IOM (2006). However, there is insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause laryngeal cancercancer of the larynx.

The Working Group noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos (Acheson *et al.*, 1982; Wignall & Fox, 1982; Germani *et al.*, 1999; Berry *et al.*, 2000; Magnani *et al.*, 2008). The conclusion received additional support from studies showing that women and girls with environmental, but not occupational exposure to asbestos (Ferrante *et al.*, 2007; Reid *et al.*, 2008, 2009) had positive, though non-significant, increases in both ovarian cancer incidence and mortality.

The Working Group carefully considered the possibility that cases of peritoneal mesothelioma may have been misdiagnosed as ovarian cancer, and that these contributed to observed excesses. Contravening that possibility is the finding that three of the studies cited here specifically examined the possibility that there were misdiagnosed cases of peritoneal mesothelioma, and all failed to find sufficient numbers of misclassified cases. The Working Group noted that the possibility of diagnostic misclassification had probably diminished in recent years because of the development of new immunohistochemical diagnostic techniques.

The conclusion of the Working Group received modest support from the findings of

non-significant associations between asbestos exposure and ovarian cancer in two case–control studies (Vasama-Neuvonen *et al.*, 1999; Langseth & Kjærheim, 2004).

And lastly, the finding is consistent with laboratory studies documenting that asbestos can accumulate in the ovaries of women with household exposure to asbestos (Heller *et al.*, 1996) or with occupational exposure to asbestos (Langseth *et al.*, 2007).

The study by Heller *et al.* (1996) was a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure. The study found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight). By contrast, only one of the 17 women without household exposure had counts in that range.

The study by Langseth *et al.* (2007) found approximately 3–4 × 105 asbestos fibres per gram (net weight) in normal ovarian tissue taken from 2/46 patients with ovarian adenocarcinoma. It is unclear how many of these fibres were verified as asbestos because it is stated in the publication that three chrysotile and one crocidolite asbestos fibres were identified in Case 1, and two anthophyllite and one chrysotile fibre were identified in Case 2. This small number of confirmed asbestos fibres in only two of the patients could be due to sample contamination. Technical caveats associated with quantification of asbestos fibre tissue burdens are discussed in Section 4 of this *Monograph* and in IOM (2006).

Further discussion of the biological plausibility of an association between asbestos exposure and ovarian cancer is to be found in Section 4 of this *Monograph*.

The Working Group noted a positive association between exposure to abestos and cancer of the pharynx, based on the fairly consistent positive findings in a series of well conducted cohort studies of populations occupationally exposed to asbestos (Selikoff & Seidman, 1991; Sluis-Cremer *et al.*, 1992; Reid *et al.*, 2004; Pira *et al.*, 2005) as well as on the positive findings of three case–control studies (Zheng *et al.*, 1992; Marchand *et al.*, 2000; Berrino *et al.*, 2003). This conclusion was further supported by the findings of the meta-analysis conducted by the IOM. While tobacco smoking and alcohol consumption are clearly the dominant risk factors for cancer of the pharynx in industrialized countries, these associations between cancer of the pharynx and asbestos remained evident in several studies when tobacco and alcohol exposures were considered. The Working Group observed that the strongest associations between asbestos exposure and cancer of the pharynx were seen in studies that specifically examined cancer of the hypopharynx, the portion of the pharynx that is located closest to the larynx. However, there is insufficient information in the published literature to discern whether there are any differences among asbestos fibre types in their ability to cause cancer of the pharynx.

The Working Group noted a positive association between exposure to abestos and cancer of the stomach, based on the positive associations between asbestos exposure and death from stomach cancer observed in several of the cohort studies with heaviest asbestos exposure (Selikoff *et al.*, 1964; Enterline *et al.*, 1987; Raffn *et al.*, 1989; Liddell *et al.*, 1997; Musk *et al.*, 2008). The conclusion was further supported by the positive dose–response relationships observed between cumulative asbestos exposure and stomach cancer mortality in several cohort studies (Selikoff & Hammond., 1979; Zhang & Wang, 1984; Liddell *et al.*, 1997; Pang *et al.*, 1997). It was supported by the results of two large and well performed meta-analyses (Frumkin & Berlin, 1988; Gamble, 2008). It received borderline support from the IOM meta-analysis of cohort

studies, and also from the IOM meta-analysis of case–control studies, which show an especially strong relationship when only extreme exposures are considered. It was supported by the comparison developed by the Working Group between standardized incidence ratios for lung cancer and stomach cancer.

Positive associations between asbestos exposure and stomach cancer and positive dose–response relationships are most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and stomach cancer, even if such an association were truly present.

[The Working Group noted that heavy occupational exposure to dust, as had likely occurred in the case of the Quebec asbestos cohort, could have been an effect modifier. Low socioeconomic status is also a potential confounder.]

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause stomach cancer. In the study by Liddell *et al.* (1997) exposure was to virtually pure chrysotile asbestos, in the study by Musk *et al.* (2008) the exposure was predominantly to crocidolite, and in most of the other published studies that observed positive associations, populations were exposed to mixtures of different asbestos fibres.

The Working Group noted a positive association between exposure to abestos and cancer of the colorectum, based on the fairly consistent findings of the occupational cohort studies, plus the evidence for positive exposure–response relationships between cumulative asbestos exposure and cancer of the colorectum consistently reported in the more detailed cohort studies (McDonald *et al.*, 1980; Albin *et al.*, 1990; Berry *et al.*, 2000; Aliyu *et al.*, 2005). The conclusion was further supported by the results of four large and well performed meta-analyses (Frumkin & Berlin 1988; Homa *et al.*, 1994; IOM, 2006; Gamble, 2008).

Positive exposure–response relationships between asbestos exposure and cancer of the colorectum appear most likely to be seen in studies of populations with prolonged heavy exposure to asbestos that had long-term follow-up, and that incorporated high-quality assessments of exposure. The less detailed assessments of exposure found in many of the published studies would have tended to bias study results towards the null, and thus impede recognition of an association between asbestos exposure and cancer of the colorectum, even if such an association were truly present.

The apparently non-positive findings of several the case–control studies are not a deterrent to this conclusion. The majority of these case–control studies incorporated relatively little information on levels of asbestos exposure; indeed, most of them considered exposure as simply a dichotomous yes/no variable. Some of the case–control studies also may be compromised by inadequate duration of follow-up. Thus, the Garabrant study (Garabrant *et al.*, 1992) may be subject to the criticism, offered by Gerhardsson de Verdier *et al.* (1992) that "the highest duration of exposure…was 'at least 15 years,' a period that may be too short to detect an elevated risk."

There is some suggestion in the literature that the association between asbestos might be stronger for colon cancer than for rectal cancer. This view is supported by the meta-analysis of Gamble (2008) which found a positive dose–response relationship for cancer of the colorectum taken together, but not for rectal cancer. It is supported also by the study of Jakobsson *et al.* (1994), which found excess of cancer of the right colon in asbestos-exposed workers, but not of the left colon.

However, there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause cancer of the colorectum. It is of note in the study by McDonald *et al.* (1980) that exposure was to virtually pure chrysotile asbestos, whereas in most of the other studies cited above, populations were exposed to mixtures of different asbestos fibres.

3. Cancer in Experimental Animals

3.1 Introduction

Asbestos is a collective name for six different types of fibres: chrysotile, crocidolite, amosite, anthophyllite, tremolite, actinolite (see Section 1). Dusts from various deposits of the same type of asbestos can cause variations in the severity of the effects observed. Erionite is a fibrous zeolite found in Central Anatolia (Turkey), and Oregon (USA) (see Section 1 of the *Monograph* on Erionite). Talc is a hydrated magnesium silicate, and talc ore may contain several other minerals including anthophyllite, tremolite, calcite, dolomite, magnesite, antigorite, quartz, pyrophyllite micas, or chlorites (see Section 1).

The definition of pathogenic fibre properties as "sufficiently long, thin, and durable" is the subject of much debate, as are the differences between the exposure–response relationships or retained dose–response relationships of asbestos fibres in man and in rats, and the potential differences in the carcinogenicity of chrysotile compared to the various amphibole asbestos types. One of the reasons for a potential difference is a difference in the biopersistence between the two asbestos groups mentioned. The biopersistence is higher in the amphibole group (Hesterberg *et al.*, 1996, 1998a, b). The rat is the main test model for fibre-induced diseases. As the removal of asbestos fibres due to biosolubility is slow compared to the lifetime of rats and hamsters, experiments with this model may not be appropriate in predicting results of risk in humans (Berry, 1999).

Critical fibre dimensions to be used in toxicology and occupational regulations were discussed by the Working Group. It is generally agreed that the carcinogenic potency of a fibre increases with fibre length. Apart from the ongoing scientific view, standards of regulated fibres, with few exceptions, are based on the WHO fibre definition: aspect ratio ≥ 3: 1, length ≥ 5 μm, diameter ≤ 3 μm.

The tested materials (asbestos and erionite) are not presented in separate tables as in many cases they were tested in parallel experiments. The reason to split the inhalation studies into two tables (Table 3.1; Table 3.2) is that in many studies, various asbestos fibres were used as positive control in studies in which man-made fibres were tested (Table 3.2). In these latter studies, normally only one asbestos concentration was used. As for intrapleural and intraperitoneal studies, Table 3.4 is separate from Table 3.5 because the studies of Stanton *et al.* (1981) (see Table 3.5) included many fibre types – which also included fibres not to be reviewed here – and was designed to investigate the effect of fibre length and fibre type on mesothelioma induction.

A general evaluation on the type of fibre application in animal studies and an evaluation of some of the asbestos studies listed in Tables 3.1–3.5 can be found in Pott (1993) and IARC (2002).

3.2 Inhalation exposure

Table 3.1 and Table 3.2 give an overview of the numerous inhalation experiments on asbestos, and a few experiments on erionite. Some of these are described more extensively below.

Bronchial carcinomas and pleural mesotheliomas have been observed in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in

tumour incidence at other sites. [The Working Group noted that in many studies, no complete histopathology was done.] All relatively short UICC asbestos preparations showed chronic effects in lung (based on fibre lenghts > 5 µm in the dust chamber) for fibres quantitatively roughly the same.

One of the first inhalation study with asbestos in rats that showed exposure–response relationships is the experiment of Wagner *et al.* (1974). Wistar rats were exposed to 10–15 mg/m^3 of one of the five UICC standard asbestos samples for 7 hours per day, mostly 5 days per week. The duration of exposure lasted from one day to 24 months. According to the reported data, in the group exposed to crocidolite for one day, lung tumours and one mesothelioma were found in 7/43 rats (16%). The corresponding exposure to chrysotile A (from Canada) resulted in lung tumours in 5/45 rats; for amosite 4/45 rats developed lung tumours and one mesothelioma. Three months of exposure to the five UICC standard asbestos samples resulted in the following thoracic tumour (mainly of the lung) incidences: chrysotile A, 44%;chrysotile B (from Zimbabwe), 53%; crocidolite, 42%; amosite, 27%; anthophyllite, 16%. Further results are listed in Table 3.1. In the 126 control rats, seven animals were also found to have lung tumours (Table 3.3). This high spontaneous lung tumour rate is a unique finding in Wistar rats. A review of unexposed control groups of many other studies shows that spontaneous lung tumours are very rare in this rat strain (Pott *et al.*, 1995; Table 3.3); on average, the incidence is less than one percent. Therefore, the very high tumour incidences described in this first inhalation study of Wagner *et al.* (1974) might be a misinterpretation of histopathological lesions because of a lack of experience at that time.

In a study conducted by Davis *et al.* (1978), five groups of Wistar rats were exposed to chrysotile (2.0, 10 mg/m^3), crocidolite (5.0, 10 mg/m^3), or amosite (10 mg/m^3). The highest tumour incidences (21–38%) were found in the chrysotile-exposed animals. This may be due to the relatively high fraction of fibres longer than 20 µm in the chrysotile dust used in this experiment. In addition to the lung tumours, extrapulmonary neoplasms included a relatively large number of peritoneal connective tissue tumours.

In a further study by Davis *et al.* (1986b), inhalation of short-fibred amosite did not produce tumours in Wistar rats (0/42). In contrast, there was a tumour incidence of 13/40 (33%) in a group exposed to long-fibred amosite. [The Working Group noted that extensive milling to produce short fibres may have altered the surface reactivity, see Section 4].

A group of 48 SPF Fischer rats was exposed to 10 mg/m^3 UICC chrysotile B by inhalation for 7 hours per day, 5 days per week, for 12 months (Wagner *et al.*, 1984b). This group served as positive controls in a study in which various man-made fibres were tested. After exposure, the animals were kept until natural death. Twelve thoracic tumours (one adenoma, 11 adenocarcinomas) were observed in 48 rats. In the untreated control group, no lung tumours were observed in 48 rats.

Smith *et al.* (1987) exposed groups of 58 female Osborne-Mendel rats to 7 mg/m^3 UICC crocidolite asbestos for 6 hours per day, for 5 days per week, for 2 years. After this treatment, rats were observed for life. The tumour incidence in rats exposed to crocidolite was 3/57 (one mesothelioma and two carcinomas). In the control group, no tumours were observed in 184 rats.

Special attention should be drawn to the crocidolite study with male Fischer rats of McConnell *et al.* (1994) because this study is very well documented. The exposure to 10 mg dust/m^3 (with 1610 WHO fibres/mL containing 236 fibres > 20 µm) for 6 h per day, 5 days per week had to be stopped after 10 months because of unexpected mortality, which was interpreted as a sign that the maximum tolerated dose had been exceeded. The number of WHO fibres per µg dry

Table 3.1 Studies of cancer in experimental animals exposed to various asbestos species and erionite (inhalation exposure)[a]

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Asbestos									
Chrysotile, Canada	86	NR	White rats 16 months or longer	6 h/d 5 d/wk 62 wk	0	10/41[c]	24		Gross *et al.* (1967)
Crocidolite	50	1105	Sprague-Dawley rats lifetime	4 h/d 4 d/w 24 mo	0	5/46	11		Reeves *et al.* (1974)
Chrysotile UICC/A	14.7	NR	Wistar rats lifetime	7 h/d 1 d	0	5/45	11		Wagner *et al.* (1974)
	12.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	16/36	44		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	8/19	42		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	19/27	70		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	11/17	65		

Table 3.1 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/B	9.7	NR	Wistar rats lifetime	7 h/d 1 d	0	1/42	2		
	12.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	18/34	53		
	10.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	5/17	29		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	3	14/23	61		
	10.1	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	11/21	52		
Crocidolite UICC	12.5	NR	Wistar rats lifetime	7 h/d 1 d	1	7/43	16		
	12.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	1	15/36	42		
	10.7	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	4/18	22		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/26	77		
	10.3	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/18	72		

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Amosite UICC	14.1	NR	Wistar rats lifetime	7 h/d 1 d	1	4/45	9		
	12.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	10/37	27		
	11.2	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	2/18	11		
	10.8	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	10/25	40		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	0	13/21	62		
Anthophyllite UICC	12.8	NR	Wistar rats lifetime	7 h/d 1 d	0	2/44	5		
	13.5	NR	Wistar rats lifetime	7 h/d 5 d/wk 3 mo	0	6/37	16		
	10.9	NR	Wistar rats lifetime	7 h/d 5 d/wk 6 mo	0	6/18	33		
	11.4	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	21/28	75		
	10.6	NR	Wistar rats lifetime	7 h/d 5 d/wk 24 mo	1	17/18	94		
Amosite UICC	10	550	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/43	5		Davis *et al.* (1978)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Crocidolite UICC	5	430	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	3/43	7		
	10	860	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	1/40	3		
Chrysotile SFA	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	1	1/40	3		Wagner *et al.* (1980)
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	4/18	22		
	10.8	430	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	8/22	36		
Chrysotile grade 7	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	1/39	3		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	5/18	28		
	10.8	1020	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	3/24	13		
Chrysotile UICC (/B)	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 3 mo	0	4/40	10		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 6 mo	0	10/18	56		
	10.8	3750	Wistar rats lifetime	7.5 h/d 5 d/wk 12 mo	0	6/23	26		

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC /A	2	390	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	9/42	21		Davis *et al.* (1978)
Chrysotile UICC /A	10	1950	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/40	38		
Chrysotile UICC	9	NR	Wistar rats lifetime	7 h/d 1 d/wk 12 mo	0	6/43	14	Peak dosing (one d/wk); no control group	Davis *et al.* (1980a)
Amosite UICC	50	NR	Wistar rats lifetime	7 h/d 1 d/w 12 mo	0	6/44	14	Peak dosing (one d/wk); no control group	
Chrysotile UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	15/43 (8 malignant, 7 benign)	35	No control group	Davis *et al.* (1980b)
Chrysotile "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	11/42 (3 maligant, 8 benign)	26	No control group	
Amosite "factory"	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/37	0	No control group	
Amosite UICC	10	NR	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	2/40	5	No control group	
Tremolite	10	1600	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	20/39	51		Davis *et al.* (1985)
Crocidolite UICC	10	1630/350[d]	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	1/28	4		Wagner *et al.* (1985)
Chrysotile WDC textile yarn	3.5	679	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	18/41	44		Davis *et al.* (1986a)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile factory WDC	3.7	468	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	21/44	48		
Chrysotile textile yarn	3.5	428	Wistar rats lifetime	7 h/d 5 /wk 12 mo	1	16/42	38		
Chrysotile experimental WDC	3.5	108	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	4	21/43	49		
Chrysotile experimental WDC reversed daylight	3.8	111	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	18/37	49		
Amosite "long"	10	2060/1110[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	13/40	33		Davis *et al.* (1986b)
Amosite "short"	10	70/12[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	0/42	0		
Crocidolite UICC	10	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	1/28	4		Wagner *et al.* (1987)
Chrysotile, Canada, "long"	10	5510/1930[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	2	22/40	55	1 peritoneal mesothelioma was observed in addition	Davis & Jones (1988)
Chrysotile, Canada, "short"	10	1170/330[d]	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	7/40	18	1 peritoneal mesothelioma was observed in addition	
Chrysotile UICC/A "discharged"	10	2670	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	1	11/39	28		Davis *et al.* (1988)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile UICC/A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	14/36	39		
Chrysotile UICC /A	10	2560	Wistar rats lifetime	7 h/d 5 d/wk 12 mo	0	13/37	35		Davis *et al.* (1991a)
Chrysotile UICC /A	10	2545	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	26/41	63	Increase of tumour rate by particulate dust	
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile UICC /A	10	1960	Wistar rats lifetime	5 h/d 5 d/w 12 mo	6	22/38	58	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	3648	Wistar rats lifetime	5 h/d 5 d/w 12 mo	2	20/40	50	Increase of tumour rate by particulate dust	Davis *et al.* (1991a)
+ titanium dioxide	+ 10	-		+ 2 h/d 5 d/w 12 mo					
Amosite "long"	10	4150	Wistar rats lifetime	5 h/d 5 d/w 12 mo	8	26/39	67	Increase of tumour rate by particulate dust	
+ quartz S600	+ 2	-		+ 2 h/d 5 d/w 12 mo					
Chrysotile Jeffrey	11	NR	Fischer rats lifetime	6 h/d 5 d/wk 12 mo	0	20/52	38		Mc Connell *et al.* (1991)

Table 3.1 (continued)

Test substance	Concentration (mg/m^3)	Aerosol fibres per mL (L > 5 µm)	Species and strain, observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[b]/ No. of animals examined	% tumours	Comments	Reference
Chrysotile	NR	NR	Baboons 6 yr	6 h/d 5 d/wk 4 years	0	0/6[e]	0		Goldstein & Coetzee (1990)
Crocidolite UICC	12-14	1130-1400	Baboons 6 yr	6 h/d 5 d/wk 4 yr	3	3/21[f]	14		
Amosite UICC	7	1110	Baboons 6 yr	6 h/d 5 d/wk 4 yr	2	2/11[f]	18		Goldstein & Coetzee (1990), Webster *et al.* (1993)
Erionite									
Erionite, Oregon	10	354	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	27	27/28	96		Wagner *et al.* (1985)
Erionite, Oregon	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	24	24/27	89	No control group	Wagner (1990)
Erionite, Oregon "short"	NR	NR	Fischer rats lifetime	7 h/d 5 d/wk 12 mo	0	0/24	0	No control group	

[a] negative control groups: see Table 3.3

[b] Animals with benign or malignant lung tumour or pleural mesothelioma. The percentage of animals with tumours is related to the number of rats examined which were alive at a certain point in time (e.g. at the beginning of the experiment or after one year, or at the point in time of the death of the first animal with a tumour). Often, this is not clearly specified.

[c] observation time ≥6 mo

[d] Fibre count refers to fibres with lengths > 10 µm and diameters < 1 µm, in the aerosol

[e] observation time ≥4 yr

[f] observation time ≥5 yr

d, day or days; h, hour or hours; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

From Pott & Roller (1993b)

Table 3.2 Studies of cancer in experimental animals in which asbestos was used as positive control group (in inhalation studies of various man-made mineral fibres)

Test substance	Concentration (mg/m^3)	Aerosol fibres per cm^3 (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Amosite	NR	981 89 f > 20 µm/cm^3	AF/HAN rats, 24 mo	7 h/d 5 d/wk 12 mo	2	18/42 (7 carcinomas, 9 adenomas)	43		Davis *et al.* (1996), Cullen *et al.* (2000)
Chrysotile UICC/B	10	NR	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	11/56 (7 adenocarcinomas, 4 adenomas)	20		McConnell *et al.* (1984)
Chrysotile UICC/B	10	3832/1513[b]	Fischer rats, lifetime	7 h/d 5 d/wk 12 mo	0	12/48 (11 adenocarcinomas, 1 adenoma)	25		Wagner *et al.* (1984b)
Chrysotile NIEHS, Canada	10	10 600	Fischer rats, 24 mo	6 h/d 5 d/wk 24 mo	1	14/69	20		Hesterberg *et al.* (1993)
Crocidolite	10	1610	Fischer 344/N rats, 24 mo	6 h/d 5 d/wk 10 mo	1	14/106 (10 adenomas, 5 carcinomas)	13		McConnell *et al.* (1994)
Crocidolite UICC	7	3000/90[b]	Osborne-Mendel rats, lifetime	6 h/d 5 d/wk 24 mo	1	3/57 (1 mesothelioma, 2 carcinomas)	5		Smith *et al.* (1987)
Chrysotile UICC/A	Cumulative dose: 13 800 mg.h/m^3	NR	Rats, lifetime	6 h/d 5 d/wk 18 mo	0	9/39 (5 adenomas, 1 adenocarcinoma, 3 squamous cell carcinomas)	23	Strain not specified	Pigott & Ishmael (1982)
Amosite UICC	300	3090	Sprague-Dawley rats, 18–24 mo	6 h/d 5 d/wk 3 mo	0	3/16[c]	19	Small number of animals; D= 0.4 µm	Lee *et al.* (1981), Lee & Reinhardt (1984)
Chrysotile, Canada	5	5901	Wistar rats, 24 mo	5 h/d 5 d/wk 12–24 mo	0	9/47	19		Le Bouffant *et al.* (1987)
Chrysotile Calidria	6	131	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	0/50	0		Muhle *et al.* (1987)

Table 3.2 (continued)

Test substance	Concentration (mg/m³)	Aerosol fibres per cm³ (L > 5 µm)	Species and strain (No. at risk); Observation time	Duration of exposure	Number of pleural mesothelioma	No. of animals with thoracic tumours[a] / No. of animals	% tumours	Comments	Reference
Crocidolite, South Africa	2.2	162	Wistar rats, 24 mo	5 h/d 4 d/wk 12 mo	0	1/50	2		Muhle *et al.* (1987)
Amosite UICC	300	3090	Syrian golden hamsters, 18–24 mo	6 h/d 5 d/wk 3 mo	0	0/12	0	Small number of animals diameter, 0.4 µm	Lee *et al.* (1981), Lee & Reinhardt (1984)
Crocidolite UICC	7	3000/90[b]	Syrian golden hamsters, lifetime	6 h/d 5 d/wk 24 mo	0	0/58	0		Smith *et al.* (1987)
Amosite	0.8	36 WHO f/cm³ 10 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	3	3/83	3.6		McConnell *et al.* (1999)
	3.7	165 WHO f/cm³ 38 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	22	22/85	26		
	7.1	263 WHO f/cm³ 69 f> 20 µm/cm³	Syrian golden hamsters, 84 wk	6 h/d 5 d/wk 78 wk	17	17/87	20		
Crocidolite UICC	13.5	1128	Baboons lifetime	7 h/d 5 d/wk 40 mo	0	0/10	0	All males	Goldstein *et al.* (1983)

[a] *n* = animals with benign or malignant lung tumour or pleural mesothelioma

[b] Number of fibres with a length > 10 µm and a diameter < 1 µm in the aerosol

d, day or days; f, fibre; h, hour or hours; mo, month or months; NR, not reported; RCF, refractory ceramic fibre; wk, week or weeks

From Pott & Roller (1993b)

Table 3.3 Negative controls (clean air for lifetime) in carcinogenicity studies after inhalation exposures from Table 3.1 and Table 3.2

Species and strain	Number of pleural mesothelioma	No. of animals with thoracic tumours[a]/ No. of animals	Reference
Fischer rats	0	0/48	Wagner *et al* (1984b)
Fischer rats	0	0/28	Wagner *et al.* (1985)
Fischer rats	0	0/28	Wagner *et al.* (1987)
Fischer rats	0	1/56	McConnell *et al.* (1991)
Fischer rats	0	4/123	Hesterberg *et al.* (1993)
Fischer rats	0	2/126	McConnell *et al.* (1994)
Osborne-Mendel rats	0	0/184	Smith *et al.* (1987)
Sprague-Dawley rats	0	1/5	Reeves *et al.* (1974)
Sprague-Dawley rats	0	0/19	Lee *et al.* (1981)
White rats	0	0/25	Gross *et al.* (1967)
Wistar rats	0	7/126	Wagner *et al.* (1974)
Wistar rats	0	0/20	Davis *et al.* (1978)
Wistar rats	0	1/71	Wagner *et al.* (1980)
Wistar rats	0	0/36	Davis *et al.* (1985)
Wistar rats	0	2/39	Davis *et al.* (1986a)
Wistar rats	0	0/25	Davis *et al.* (1986a)
Wistar rats	0	0/110	Muhle *et al.* (1987)
Wistar rats	0	2/36	Davis *et al.* (1988)
Wistar rats	0	0/25	Davis *et al.* (1988)
Wistar rats	0	2/47	Davis & Jones (1988)
Wistar rats	0	2/47	Davis *et al.* (1991a)
Syrian golden hamsters	0	1/170	Smith *et al.* (1987)
Syrian golden hamsters	0	0/83	Mc Connell *et al.* (1999)

[a] *n* = animals with benign or malignant lung tumour or pleural mesothelioma

lung tissue was 1850 (73 fibres > 20 µm) at the end of exposure and 759 WHO fibres (41 fibres > 20 µm) 12 months later. Fourteen out of 106 rats (13.2%), which survived the second year or longer, died with lung tumour (five of these rats developed lung carcinomas), and one rat also developed a mesothelioma. In the control group, 2/126 rats developed lung adenomas.

In two lifetime studies, male and female Fischer rats were exposed to either 10 mg/m^3 erionite (Wagner *et al.*, 1985) or an unknown concentration of erionite (Wagner, 1990) for 6 hours per day, 5 days per week, for 12 months. Twenty seven out of 28 rats, and 24/27 rats developed pleural mesotheliomas, respectively. No lung tumours were observed. [The Working Group noted the lack of control group in the study by Wagner (1990).]

McConnell *et al.* (1999) exposed three groups of 125 male Syrian golden hamsters to 0.8, 3.7 and 7.1 mg/m^3 amosite for 6 hours per day, 5 days per week, for 78 weeks. They were then held unexposed for 6 weeks. Among animals that survived for at least 32 weeks, 3/83, 22/85 and 17/87 developed pleural mesotheliomas, respectively. No mesotheliomas were observed in 83 untreated controls and no lung tumours were observed in any groups.

Some experiments were reported with baboons. After amosite exposure and crocidolite exposure for 4 years, 2/11 baboons and 3/21 baboons developed pleural mesothelioma,

respectively (Goldstein & Coetzee, 1990; Webster *et al.*, 1993).

3.3 Intrapleural and intraperitoneal administration

Animal experiments had shown that an intrapleural injection of a suspension of asbestos dusts in rats leads to mesotheliomas (Wagner, 1962; Wagner & Berry, 1969). The serosa has subsequently been taken as a model for the examination of the carcinogenicity of fibrous dusts in numerous studies. Some groups have opted for administration into the pleural cavity, others preferring intraperitoneal injection of dust suspensions. In comparison with the intrapleural model, the intraperitoneal carcinogenicity test on fibres has proven to be the method with the far greater capacity and, consequently, the greater sensitivity (see also Pott & Roller, 1993a). Results from these numerous experiments using asbestos and erionite are listed in Table 3.4.

Table 3.5 contains a summary of the experiments by Stanton *et al.* (1981). In this extensive study, the authors implanted 72 dusts containing fibres of various sizes in the pleura of Osborne-Mendel rats. The probability of the development of pleural mesotheliomas was highest for fibres with a diameter of less than 0.25 µm and lengths greater than 8 µm.

In summary, samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelima induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

3.4 Intratracheal administration

Only a few studies have been carried out with intratracheal instillation of asbestos fibres in rats (Pott *et al.*, 1987; Smith *et al.*, 1987), and hamsters (Pott *et al.*, 1984; Feron *et al.*, 1985; Smith *et al.*, 1987). Principally, in this experimental model, asbestos fibres induced lung tumours in rats, and lung tumours and mesotheliomas in hamsters. Studies in hamsters are described below.

In a 2-year study, a group of male Syrian golden hamsters [initial number unspecified] was intratracheally instilled with 1 mg UICC crocidolite in 0.15 mL saline once a week for 8 weeks. At the end of the experiment, the incidences of lung carcinomas and of pleural mesotheliomas were 9/142 [$P < 0.01$] and 8/142 [$P < 0.01$], respectively. No thoracic tumours were observed in 135 titanium-dioxide-treated control animals (Pott *et al.*, 1984).

In a lifetime study, a group of Syrian golden hamsters [sex and initial number unspecified] was intratracheally instilled with 2 mg UICC crocidolite in 0.2 mL saline once a week for 5 weeks. At the end of the experiment, 20/27 animals developed broncho-alveolar tumours ($p<0.05$), including 7/27 with malignant tumours [$p<0.05$]. No broncho-alveolar tumours were observed in 24 saline-treated controls (Smith *et al.*, 1987).

3.5 Oral administration

A study on the carcinogenicity of ingested asbestos fibres involved male F344 rats groups exposed to amosite or chrysotile in combination with subcutaneous administration of a known intestinal carcinogen, azoxymethane (10 weekly injections of 7.4 mg/kg body weight). Fibres were administered three times a week for 10 weeks by intragastric bolus dosing (10 mg in 1 mL saline). The first experiment in this study included a full set of appropriate control groups. The experiment was terminated at 34 weeks. Neither amosite nor UICC chrysotile B, in combination with azoxymethane, increased the incidence of any intestinal tumours (≈10%) above that produced by azoxymethane alone, but the combination with either fibre type produced 4–5-fold increases

(not significant, $P > 0.1$) in metastatic intestinal tumours. A second experiment with larger groups, the same dosing regimen, and for lifetime, but with a more limited design, tested only amosite in combination with azoxymethane versus azoxymethane. Amosite did not enhance azoxymethane-induced intestinal tumours (incidence, 77% versus 67%) (Ward *et al.*, 1980; IOM, 2006). [The Working Group noted that the lack of untreated vehicle controls in the second experiment made interpretation of the results difficult considering that, compared to historical controls, there was a non-significant increase in intestinal tumours in rats exposed only to amosite (≈33%). One cannot know whether the results observed were associated with the asbestos or with irritation from the procedure, although one would not anticipate that gavage itself would impact the lower portion of the gastrointestinal tract.]

The most definitive animal studies of oral exposure to asbestos were a series of lifetime studies conducted by the National Toxicology Program (NTP, 1983, 1985, 1988, 1990a, b), in which asbestos (chrysotile, crocidolite, and amosite) was administered in the feed of rats and hamsters. Nonfibrous tremolite was also tested in rats according to the same protocol (NTP, 1990c). Exposure of dams of the study animals (1% in the diet) was followed by exposure of the pups by gavage (0.47 mg/g water) while they were nursing, and then in the diet for the remainder of their lives: they were exposed to asbestos at the level of 1%, which was estimated by the investigators to be about 70000 times the greatest possible human exposure in drinking-water. Histopathological examination of the entire colorectum was performed. No increases in the incidence of gastrointestinal lesions (inflammatory, preneoplastic, or neoplastic) were found after exposure to intermediate-length chrysotile (from Quebec) in hamsters, to short chrysotile (from New Idria) in rats or hamsters, to amosite in rats or hamsters, to crocidolite in rats, or to non-fibrous tremolite in rats. The mesentery was examined in detail, as well as mesenteric lymph nodes and sections of the larynx, trachea, and lungs from every animal. No lesions were found in any of those tissues. The only finding of note in the gastrointestinal tract was a slight increase in the incidence of adenomatous polyps in the large intestine after exposure to the intermediate-length chrysotile (from Quebec) in male rats (9/250 versus 0/85, $P = 0.08$), but preneoplastic changes in the epithelium were not found (NTP, 1985; IOM, 2006).

3.6 Intragastric administration

White rats, 2–3 months old, were surgically applied, on the greater curvature of the stomach, a perforated capsule containing 0 (control) or 100 mg chrysotile asbestos in a filler (beef fat: natural wax, 1:1). Tumours observed in 18/75 asbestos-exposed rats, between 18–30 months after the beginning of the experiment, were the following: eight gastric adenomas, two gastric adenocarcinomas, one gastric carcinoma, one cancer of the forestomach, one small intestine adenocarcinoma, two peritoneal mesotheliomas, and three abdominal lymphoreticular sarcomas. No tumours were observed in 75 control animals (Kogan *et al.*, 1987). [The Working Group noted various unresolved questions regarding the design of this study in particular the very high dose of 100 mg.]

3.7 Studies in companion animals

Mesotheliomas were reported in pet dogs with asbestos exposure in the households of their owners. Eighteen dogs diagnosed with mesothelioma and 32 age-, breed- and gender-matched control dogs were investigated. Sixteen owners of cases and all owners of controls were interviewed. An asbestos-related occupation or hobby of a household member was significantly associated with mesothelioma observed in cases (OR,

Table 3.4 Studies of cancer in rats exposed to asbestos fibres and erionite (intrapleural and intraperitoneal administration)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Asbestos	**Asbestos type**							
Wistar – Pott *et al.* (1989)	Actinolite	0.25	i.p.	0.1	20/36	56	***	
Wistar – Wagner *et al.* (1973)	Amosite UICC	20	i.pl.	NR	11/32	34	***	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.01	i.p.	0.0003	4/48	8	*	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.05	i.p.	0.002	8/32	25	***	
Wistar – Davis *et al.* (1991b)	Amosite from UICC	0.5	i.p.	0.02	15/32	47	***	
Wistar – Wagner *et al.* (1973)	Anthophyllite UICC	20	i.pl.	NR	8/32	25	***	
Wistar – Wagner *et al.* (1973)	Chrysotile UICC/A	20	i.pl.	NR	7/31	23	***	
Sprague-Dawley – Monchaux *et al.* (1981)	Chrysotile UICC/A	20	i.pl.	NR	14/33	42	***	
Sprague-Dawley – Wagner *et al.* (1984b)	Chrysotile UICC/A	20	i.pl.	19.6	6/48	13	**	
Wistar – Pigott & Ishmael (1992)	Chrysotile UICC/A	20	i.pl.	NR	7/48	15	***	
Fischer – Coffin *et al.* (1992)	Chrysotile UICC/A	0.5	i.pl.	0.90	118/142 [d]	78	***d	
		2		3.6		87		
		4		7.2		92		
		8		14		83		
		16		29		83		
		32		57		75		
Wistar – Wagner *et al.* (1973)	Chrysotile UICC/B	20	i.pl.	NR	10/32	31	***	
Wistar – Wagner *et al.* (1980)	Chrysotile UICC/B	20	i.pl.	NR	5/48	10	*	
Fischer – Wagner *et al.* (1987)	Chrysotile UICC/B	20	i.pl.	NR	19/39	49	***	
Wistar – Pott *et al.* (1989)	Chrysotile UICC/B	0.25	i.p.	0.2	23/34	68	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.01	i.p.	0.002	2/48	4	NS	
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.05	i.p.	0.009	12/32	38	***	
Wistar – Davis *et al.* (1991b)	Chrysotile from UICC/A	0.5	i.p.	0.09	26/32	81	***	
Wistar – Wagner *et al.* (1973)	Crocidolite UICC	20	i.pl.	NR	19/32	59	***	
Fischer – Wagner *et al.* (1987)	Crocidolite UICC	20	i.pl.	NR	34/40	85	***	
Fischer – Wagner (1990)	Crocidolite UICC	20	i.pl.	NR	24/32	75	***	
Sprague-Dawley – Monchaux *et al.* (1981)	Crocidolite UICC	20	i.pl.	NR	21/39	54	***	
Osborne-Mendel – Stanton *et al.* (1981)	Crocidolite UICC	40	i.pl.	NR	14/29	48	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC	20	i.pl.	NR	35/41	85	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 1 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 2 h	20	i.pl.	NR	34/42	81	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 4 h	20	i.pl.	NR	15/41	37	***	
Fischer – Wagner *et al.* (1984a)	Crocidolite UICC ground 8 h	20	i.pl.	NR	13/42	31	***	
Fischer – Coffin *et al.* (1992)	Crocidolite UICC	0.5	i.pl.	0.04	65/144[d]	29	** [d]	
		2		0.16		13		
		4		0.32		50		
		8		0.65		67		
		16		1.3		58		
		32		2.6		54		
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.01	i.p.	0.0004	0/48	0	NS	
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.05	i.p.	0.002	8/32	25	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Wistar – Davis *et al.* (1991b)	Crocidolite from UICC	0.5	i.p.	0.02	10/32	31	***	
Wistar – Pott *et al.* (1987)	Crocidolite South Africa	0.5	i.p.	0.05	18/32	56	***	
Wistar – Roller *et al.* (1996)	Crocidolite A	0.5	i.p.	0.042	25/32	78	***	All females
Wistar – Roller *et al.* (1996)	Crocidolite A	0.5	i.p.	0.042	32/48	67	***	All females
Wistar – Roller *et al.* (1996)	Crocidolite C	0.5	i.p.	0.042	20/39	51	***	
Wistar – Davis *et al.* (1985)	Tremolite, Korea	25	i.p.	NR	27/29	93	***	
Wistar – Roller *et al.* (1996)	Tremolite B	3.3	i.p.	0.057	9/40	23	***	
Wistar – Roller *et al.* (1996)	Tremolite B	15	i.p.	0.26	30/40	75	***	
Erionite	Erionite type							
Sprague-Dawley – Pott *et al.* (1987)	Karain	1.25	i.p.	NR	38/53	72	***	
Sprague-Dawley – Pott *et al.* (1987)	Karain	5	i.p.	NR	43/53	81	***	
Sprague-Dawley – Pott *et al.* (1987)	Karain	20	i.p.	G	37/53	70	***	
Fischer – Wagner *et al.* (1985)	Karain	20	i.pl.	NR	38/40	95	***	
Fischer – Wagner *et al.* (1985)	Oregon	20	i.pl.	NR	40/40	100	***	
Wistar – Pott *et al.* (1987)	Oregon	0.5	i.p.	0.02	15/31	48	***	
Wistar – Pott *et al.* (1987)	Oregon	2	i.p.	0.08	28/31	90	***	
Fischer – Wagner (1990)	Oregon	20	i.pl.	NR	30/32	94	***	
Fischer – Wagner (1990)	Oregon "short"	20	i.pl.	NR	0/32	0	NS	
Wistar – Davis *et al.* (1991b)	Oregon	0.005	i.p.	0.00025	0/48	0	NS	
		0.01		0.0005	4/48	8	*	
		0.05		0.0025	15/32	47	***	
		0.5		0.025	26/32	81	***	
		2.5		0.125	30/32	94	***	
		5		0.25	21/24	88	***	
		10		0.5	20/24	83	***	
		25		1.25	17/18	94	***	

Table 3.4 (continued)

Rat strain Reference	Fibrous dust (material)	Injected mass (mg)	Injection type	No. of fibres [a] [10^9]	Tumour incidence [b]		Significance [c]	Comments
					n/z	%		
Porton – Hill *et al.* (1990)	Oregon	0.1	i.pl.	NR	5/10	50	*	
		1		NR	9/10	90	***	
		10		NR	9/10	90	***	
		20		NR	8/10	80	***	
Wistar – Kleymenova *et al.* (1999)	Grusia mines	20	i.pl.	NR	39/40	98	?	
Fischer – Coffin *et al.* (1992)	Oregon "C"	0.5	i.pl.	NR	123/144[d]	79	***[d]	
		2		NR		87		
		4		NR		83		
		8		NR		84		
		16		NR		87		
		32		NR		91		
Fischer – Coffin *et al.* (1992)	Oregon "W"	0.5	i.pl.	NR	137/144[d]	100	***[d]	
		2		NR		92		
		4		NR		100		
		8		NR		91		
		16		NR		96		
		32		NR		92		
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.pl.	NR	35/40	88	***	
Sprague-Dawley – Maltoni & Minardi (1989)	"Sedimentary erionite"	25	i.p.	NR	35/40	50	***	

[a] The fibre numbers mainly refer to fibres with a length greater than 5 µm
[b] n/z number of animals with serosal tumour (mesothelioma/sarcoma) / number of animals examined
[c] calculation of the statistical significance with the Fisher exact test, one-sided: *** $p < 0.001$; ** $p < 0.01$; * $p \leq 0.05$
[d] combined data of 6 groups
i.p., intrapleural; i.pl., intraperitoneal; NS, not significant; NR, not reported
From Pott & Roller (1993b)

Table 3.5 Carcinogenicity study of intrapleural application of asbestos fibres and other fibrous materials in female Osborne-Mendel rats (40 mg fibres per rat)

Fibrous dust (material)	No. of fibres [a] ($x10^6$) L > 8 µm D < 0.25 µm	Probability of pleural sarcomas [b]		Pleural sarcoma incidence [c]	
				n/z	%
Tremolite 1	55	100		22/28	79
Tremolite 2	28	100		21/28	75
Crocidolite 1	6500	94	± 6.0	18/27	67
Crocidolite 2	800	93	± 6.5	17/24	71
Crocidolite 3	4100	93	± 6.9	15/23	65
Amosite	140	93	± 7.1	14/25	56
Crocidolite 4	5400	86	± 9.0	15/24	63
Crocidolite 5 (UICC)	78	78	± 10.8	14/29	48
Crocidolite 6	1600	63	± 13.9	9/27	33
Crocidolite 7	18	56	± 11.7	11/26	42
Crocidolite 8	< 0.3[d]	53	± 12.9	8/25	32
Crocidolite 9	710	33	± 9.8	8/27	30
Crocidolite 10	49	37	± 13.5	6/29	21
Crocidolite 11	< 0.3[d]	19	± 8.5	4/29	14
Crocidolite 12	220	10	± 7.0	2/27	7
Talc 1	< 0.3[d]	7	± 6.9	1/26	4
Talc 3	< 0.3[d]	4	± 4.3	1/29	3
Talc 2	< 0.3[d]	4	± 3.8	1/30	3
Talc 4	< 0.3[d]	5	± 4.9	1/29	3
Crocidolite 13	< 0.3[d]	0		0/29	0
Talc 5	< 0.3[d]	0		0/30	0
Talc 6	80	0		0/30	0
Talc 7	< 0.3[d]	0		0/29	0

[a] Fibre numbers stated in original work as common logarithm.

[b] Calculation taking into account the different life spans (life table method).

[c] n/z = number of rats with pleural sarcomas/number of rats examined. Frequency of pleural sarcomas in female control rats: untreated, 3 animals out of 491 (0.6%); with non-carcinogenic lung implantates, 9 out of 441 (2.0%); with non-carcinogenic pleural implantates, 17 out of 615 (2.8%). [17 out of 615 against 3 out of 491, according to Fisher exact test $P < 0.01$]. All three control groups are brought together by Stanton *et al.* (1981) to 29 out of 1518 animals (1.9%); for this after application of the life table method a tumour probability of 7.7 ± 4.2% is indicated. [Without any reason being given it is concluded that the tumour probability in any one of the groups treated according to the life table method must exceed 30% to be "significantly" increased.] Significance limit for Fisher test in the case of 25 to 30 animals against 17 out of 615 control rats: approx. 12 to 13% tumour frequency. (The term "tumour frequency" is not to be equated with tumour probability according to the life table method. The "significance limit" of 30% mentioned by Stanton *et al.* (1981) refers to life table incidence or probability.

[d] The de-logarithmised fibre numbers with the above mentioned definition are between 0 and 0.3.

From Stanton *et al.* (1981)

8.0; 95%CI: 1.4–45.9). Lung tissue from three dogs with mesothelioma and one dog with squamous cell carcinoma of the lung had higher level of chrysotile asbestos fibres than lung tissue from control dogs (Glickman *et al.*, 1983).

3.8 Synthesis

Bronchial carcinomas and pleural mesotheliomas were observed in many experiments in rats after exposure to chrysotile, crocidolite, amosite, anthophyllite, and tremolite fibres. In these studies, there was no consistent increase in tumour incidence at other sites. A special preparation of "long" crocidolite was more effective to induce lung tumours compared to the "short" UICC asbestos samples on the basis of administered dose in f/mL.

In one study in Syrian golden hamsters with three different concentrations of amosite, a significant increase in pleural mesothelioma incidence was observed, but no lung tumours were found.

After amosite exposure and crocidolite exposure by inhalation, 2/11 baboons and 3/21 baboons developed pleural mesothelioma, respectively.

In two studies in rats exposed to erionite, a significant increase in pleural mesothelioma incidence was observed. However, no lung tumours were found.

Samples of all six asbestos types and of erionite were administered to rats by intrapleural or intraperitoneal injection in numerous studies. Consistently, mesothelioma induction was observed when samples contained a sufficient fibre number with a fibre length > 5 µm.

Only a few studies have been carried out with intratracheal instillation of crocidolite in rats and hamsters. Malignant lung tumours were observed in rats, and pleural mesothelioma and malignant lung tumours were observed in hamsters.

Chrysolite, crocidolite and amosite were administered in the feed of rats and hamsters. No increase of the incidence of gastrointestinal tumours was observed in both species.

No chronic studies with vermiculite containing asbestos fibres or talc containing asbestos fibres could be identified.

4. Other Relevant Data

4.1 Toxicokinetics, deposition, clearance, and translocation in humans

4.1.1 Aerodynamic and anatomical factors

Inhalation is the most important route of exposure to mineral fibres, and is associated with the development of non-malignant diseases of the lungs and pleura, and malignant diseases arising in the lung, larynx, and pleural and peritoneal linings (IOM, 2006). The deposition of particles and fibres in the lungs is dependent on their aerodynamic diameter, which is a function of geometry, aspect ratio (IARC, 2002), and density (Bernstein *et al.*, 2005). Fibres can deposit by sedimentation, by impaction at bronchial bifurcations or by interception of the fibre tip with the bronchial wall. Smaller diameter fibres are likely to deposit in the alveoli (Bernstein *et al.*, 2005).

Particles and fibres can be cleared from the nasal and tracheobronchial regions by mucociliary transport (Lippmann *et al.*, 1980). Following deposition in the distal airways and alveoli, short fibres are removed more slowly following phagocytosis by alveolar macrophages. Fibre length is a limiting factor in macrophage-mediated clearance; fibres longer than the diameter of human alveolar macrophages (approximately 14–25 µm) are less likely to be cleared. Fibres may also interact with lung epithelial cells, penetrate into the interstitium, and translocate to the pleura and peritoneum or more distant sites. Fibres that are not efficiently cleared or altered by physicochemical process (e.g. breakage, splitting, or

chemical modification) are termed biopersistent (Bernstein *et al.*, 2005). Chronic inhalation assays using man-made fibres in rodents have correlated fibre length and biopersistence with persistent inflammation, fibrosis, lung cancer, and malignant mesothelioma (Bernstein *et al.*, 2005). However, there are interspecies differences in alveolar deposition of inhaled particles and fibres that must be considered when extrapolating results of rodent inhalation studies to humans (IARC, 2002).

4.1.2 Biopersistence of asbestos and erionite fibres

Asbestos fibres and ferruginous bodies (described subsequently in Section 4.3.1) can be identified and quantified by tissue digestion of lung samples obtained by biopsy or at autopsy (Roggli, 1990). A variety of commercial and non-commercial asbestos fibres have been identified in residents older than 40 years of age living in an urban area with no history of occupational asbestos exposure (Churg & Warnock, 1980). These and other studies confirm that asbestos fibres are biopersistent and accumulate in lung tissue as well as lymph nodes (Dodson *et al.*, 1990; Dodson & Atkinson, 2006). Asbestos fibres have also been identified in the pleura following autopsy (Dodson *et al.*, 1990; Gibbs *et al.*, 1991; Suzuki & Yuen, 2001) and in the parietal pleural in samples collected during thoracoscopy (Boutin *et al.*, 1996). Roggli *et al.* (1980) also identified asbestos bodies in the larynx of asbestos workers at autopsy. Systemic translocation of asbestos fibres to distant organs has also been described in case reports; however, these reports should be evaluated with caution due to the numerous caveats in technical procedures used, comparison with an appropriate control population, and cross-contamination of tissue samples (Roggli, 2006). The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals (Hesterberg *et al.*, 1999; Mc Connell *et al.*, 1999; IOM, 2006; NIOSH, 2009).

Environmental exposure to erionite fibres is associated with diffuse malignant mesothelioma in three rural villages in the Cappadocia region of Turkey (Baris & Grandjean, 2006). Lung fibre digests obtained from humans in these villages showed elevated levels of erionite fibres, and ferruginous bodies surrounding erionite fibres were found in broncho-alveolar lavage fluid (Sébastien *et al.*, 1984; Dumortier *et al.*, 2001).

Talc particles have been found in the lungs at autopsy of both rural and urban residents as well as talc miners (IARC, 1987b, 2010). Talc particles are biopersistent in the lungs, and have been recovered in broncho-alveolar lavage fluid obtained from workers 21 years after cessation of occupational exposure (Dumortier *et al.*, 1989). Talc contaminated with asbestos has been linked to the development of lung cancer and malignant mesothelioma (IARC, 1987b).

The association between exposure to talc, potential retrograde translocation to the ovarian epithelium, and the development of ovarian cancer is controversial (IARC, 2010, and this volume).

The biological plausibility for an association between asbestos and ovarian cancer derives in part from the finding of asbestos fibres in the ovaries of women with potential for exposure to asbestos. Thus, a histopathological study of ovaries from 13 women who had household contact with men who had documented exposure to asbestos, and of 17 women who gave no history of potential for asbestos exposure found "significant asbestos fibre burdens" in the ovaries of nine (60.2%) of the exposed women and in only six (35%) of the unexposed women. Three of the exposed women had asbestos fibre counts in ovarian tissue of over 1 million fibres per gram (wet weight), but only one of the 17

women without exposure had counts in that range (Heller *et al.*, 1996).

Further support for the biological plausibility of an association between asbestos exposure and ovarian cancer derives from an experimental study (Graham & Graham, 1967) that found that the intraperitoneal injection of tremolite asbestos into guinea-pigs and rabbits produced epithelial changes in the ovaries "similar to those seen in patients with early ovarian cancer".

[The Working Group noted that the histopathological diagnosis of ovarian carcinoma is difficult and requires the application of immunohistochemical techniques to distinguish between this cancer and peritoneal malignant mesothelioma. These techniques and the recognition of borderline ovarian tumours and variants of serosal tumours that arise in the pelvis of women were not applied in the Graham & Graham study in 1967. In addition, mesothelial hyperplasia occurs commonly in the pelvic region, and is not considered a preneoplastic lesion (NIOSH, 2009).]

4.2 Molecular pathogenesis of human cancers related to mineral dust exposure

Cancers develop in the upper and lower respiratory tract (carcinoma of the larynx and lungs), and in the pleural and peritoneal linings (diffuse malignant mesothelioma) after a long latent period up to 20–40 years following initial exposure to asbestos or erionite fibres (IARC, 1977; IOM, 2006). During the long latent period before the clinical diagnosis of cancer of the lung or of the larynx or diffuse malignant mesothelioma, multiple genetic and molecular alterations involving the activation of cell growth regulatory pathways, the mutation or amplification of oncogenes, and the inactivation of tumour–suppressor genes characterize specific histopathological types of these tumours that have been associated with exposure to mineral dust or fibres. Some of these molecular alterations have been linked to specific chemical carcinogens in tobacco smoke (Nelson & Kelsey, 2002), and additional alterations may arise secondarily due to chronic inflammation, genetic instability, or epigenetic changes that will be discussed in detail in Section 4.3.

Additional pathways related to resistance to apoptosis, acquired genetic instability, and angiogenesis are activated or upregulated during the later stages of tumour progression of lung cancer and diffuse malignant mesothelioma (Table 4.1; Table 4.2). No mutations in oncogenes or tumour-suppressor genes have been directly linked with exposure to asbestos fibres (NIOSH, 2009).

4.2.1 Cancer of the lung and of the larynx

Lung cancers are classified into two histological subtypes: small cell carcinoma and non-small cell carcinoma (Table 4.1). In non-small cell lung carcinoma, activating point mutations in the *K-RAS* oncogene have been linked to specific chemical carcinogens in tobacco smoke; Nelson *et al.* (1999) described more frequent *K-RAS* mutations in lung carcinomas in asbestos-exposed workers. Loss of heterozygosity and point mutations in the *p53* tumour-suppressor gene have also been linked with tobacco smoke carcinogens in cancer of the lung and of the larynx (Pfeifer *et al.*, 2002; NIOSH, 2009). These alterations have also been described in lung cancers in asbestos-exposed workers (Nymark *et al.*, 2008).

4.2.2 Diffuse malignant mesothelioma

Malignant tumours arising in the pleural or peritoneal linings (diffuse malignant mesothelioma) have no association with tobacco smoking, and are characterized by a different spectrum of molecular alterations (Table 4.2). In contrast with lung cancers associated with tobacco smoking and asbestos exposure, mutations in the *K-RAS*

Table 4.1 Some reported molecular alterations in bronchogenic carcinoma

Functional alterations	Gene target	Histological type of lung cancer	
		Small cell	Non-small cell
Autocrine growth stimulation	Growth factors and receptors	GRP/GRP receptor SCF/KIT	TGF-α/EGFR HGF/MET
Activation of oncogenes	*RAS* mutation	<1%	15–20%
	MYC overexpression	15–30%	5–10%
Inactivation of tumour-suppressor genes	*p53* mutation	~90%	~50%
	RB mutation	~90%	15–30%
	$p16^{INK4A}$ inactivation	0–10%	30–70%
	FHIT inactivation	~75%	50–75%
Resistance to apoptosis	*BCL2* expression	75–95%	10–35%
Genetic instability	Microsatellite instability	~35%	~22%

EGFR, epidermal growth factor receptor; FHIT, fragile histidine triad; GRP, gastrin-releasing peptide; HGF, hepatocyte growth factor; RB, retinoblastoma gene; SCF, stem cell factor; TGF-α, transforming growth factor-α.
From Sekido *et al.* (2001), Sato *et al.* (2007), Schwartz *et al.* (2007), NIOSH (2009)

oncogene or the *p53* tumour-suppressor gene are rare. The most frequent molecular alteration involves deletion or hypermethylation at the *CDKN2A/ARF* locus on chromosome 9p21 which contains three tumour-suppressor genes: *p15*, $p16^{INK4A}$, and $p14^{ARF}$ (Murthy & Testa, 1999). Additional molecular alterations include hypermethylation and silencing of the *RASSFIA* and *GPC3* tumour-suppressor genes, and inactivation of the *NF2* tumour-suppressor gene (Apostolou *et al.*, 2006; Murthy *et al.*, 2000).

Comparative genomic hydrizidation, gene expression profiling, and proteomics have been used to identify specific diagnostic and prognostic biomarkers for diffuse malignant mesothelioma (Wali *et al.*, 2005; Greillier *et al.*, 2008). The most promising outcome of these global screening strategies is the identification of two potential serum or pleural fluid biomarkers that may provide early diagnosis of malignant pleural mesothelioma: osteopontin (Pass *et al.*, 2005), and soluble mesothelin-related protein (Robinson *et al.*, 2005). Both of these markers have been shown to be elevated in most patients diagnosed with diffused malignant mesothelioma, but are not entirely specific for these cancers (Greillier *et al.*, 2008). No gene expression signature can be attributed directly to asbestos exposure, and these studies show variable gene expression patterns resulting from limited stability of RNA, contamination of tumour samples with host cells, and use of different microarray platforms (López-Ríos *et al.*, 2006).

In addition to the genetic and chromosomal alterations that have been identified in diffuse malignant mesothelioma (Table 4.2), epigenetic alterations characterized by altered patterns of DNA methylation have been described (Toyooka *et al.*, 2001; Tsou *et al.*, 2005). Overall, human tumours have been characterized by global hypomethylation associated with hypermethylation of CpG islands in the promoter regions of tumour-suppressor genes leading to their inactivation. These alterations in DNA methylation are the most common molecular or genetic lesion in human cancer (Esteller, 2005). Recent comprehensive analyses of epigenetic profiles of 158 patients with malignant pleural mesotheliomas and 18 normal pleural samples using 803 cancer-related genes revealed classes of methylation profiles in malignant mesothelioma that were associated with asbestos lung burden and survival (Christensen *et al.*, 2009). Other data confirmed hypermethylation of cell-cycle

Table 4.2 Some reported molecular alterations in diffuse malignant mesothelioma

Function	Gene target	Alteration
Autocrine growth stimulation	Growth factors and receptors	HGF/MET upregulation EGFR upregulation PDGF upregulation IGF-1 upregulation
Tumour-suppressor genes	*p15, p16^{INK4A}, p14^{ARF}*	Inactivation or deletion
	Neurofibromin 2	*NF2* deletions, mutations
	RASSF1A, GPC3	Hypermethylation
Angiogenesis	VEGF	Upregulation
Apoptosis	*AKT*	Constitutive activation
	BCL-X	Upregulation

EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; PDGF, platelet-derived growth factor; RASSF1A, Ras-association domain family 1; VEGF, vascular endothelial growth factor

From Murthy & Testa (1999), Altomare *et al.* (2005), Catalano *et al.* (2005), Kratzke & Gazdar (2005), Cacciotti *et al.* (2006), NIOSH (2009)

regulatory genes as well as inflammation-associated genes and apoptosis-related genes (Tsou *et al.*, 2007; Christensen *et al.*, 2008). Christensen *et al.* (2009) hypothesized that hypermethylation of specific genes confers a selective survival advantage to preneoplastic mesothelial cells in a microenvironment of persistent tissue injury and/or oxidative stress associated with exposure to asbestos fibres.

In summary, these new genomic and proteomics approaches offer promise for the discovery of novel biomarkers associated with the development of diffuse malignant mesothelioma following exposure to asbestos or erionite. No specific marker is yet available to identify those cancers.

4.3 Mechanisms of carcinogenesis

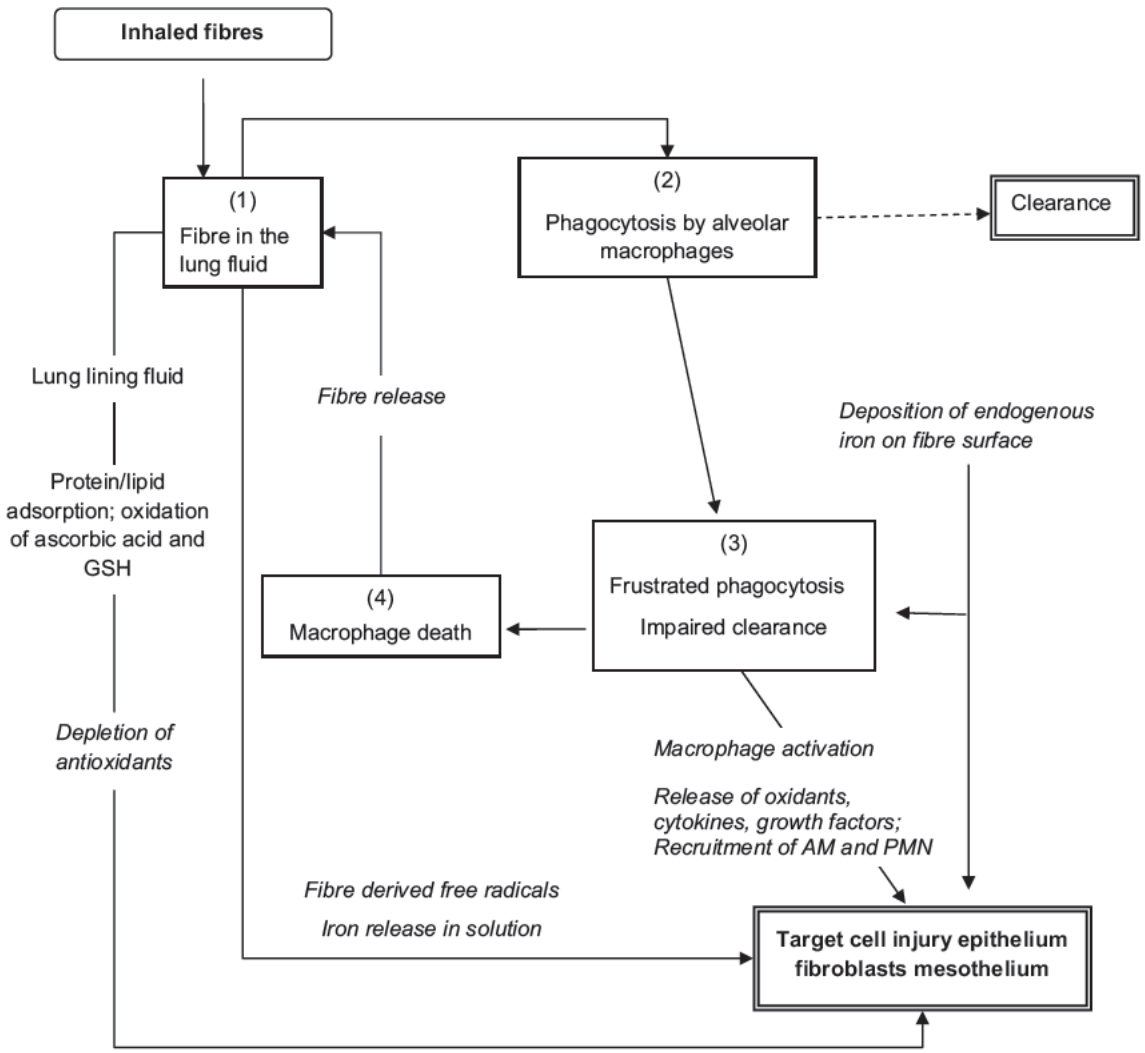
4.3.1 Physicochemical properties of mineral fibres associated with toxicity

Asbestos are natural fibrous silicates, with similar chemical composition (silica framework includes various metal cations, typically Mg^{2+}, Ca^{2+}, $Fe^{2+/3+}$, Na^{+}) mostly differing in the crystallographic constraints that yield the fibrous habit. They are poorly soluble minerals which only undergo selective leaching and incongruent dissolution. Erionite is a zeolite, which often crystallizes in thin long fibres. Major determinants of toxicity are form and size of the fibres, surface chemistry, and biopersistence. Crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, modulate surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids influence their biopersistence, a factor which modulates cumulative exposure (Fubini, 1997; Bernstein *et al.*, 2005; Fubini & Fenoglio, 2007; Sanchez *et al.*, 2009; Fig. 4.1).

(a) Crystal structure

Asbestos minerals can be divided into two groups: serpentine asbestos (chrysotile [$Mg_3Si_2O_5(OH)_4$]), and amphibole asbestos (crocidolite [$Na_2(Mg,Fe^{2+})_3Fe_2^{3+}Si_8O_{22}(OH)_2$], amosite [$(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$], tremolite [$Ca_2Mg_5Si_8O_{22}(OH)_2$], actinolite [$Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2$], and anthophyllite [$Mg_7Si_8O_{22}(OH)_2$]). Formulae reported are ideal and are always significantly modified in nature by the occurrence of several substituting cations (e.g. $Fe^{2+/3+}$, Al^{3+}, Na^{+}). The crystal structure of chrysotile results from the association of a tetrahedral silicate sheet of composition $(Si_2O_5)_n^{2n-}$ with an octahedral brucite-like sheet of composition $[Mg_3O_2(OH)_4]_n^{2n+}$, in which iron substitutes for magnesium. The two sheets are bonded to form a 1:1 layer silicate; a slight misfit between the sheets causes curling to form

Fig. 4.1 Physicochemical properties involved in the biological activity of asbestos fibres



AMs, alveolar macrophages; GSH, glutathione; PMNs, polymorphonuclear neutrophils
Adapted from Fubini & Otero Areán (1999), Fubini & Fenoglio (2007)

concentric cylinders, with the brucite-like layer on the outside. Van der Waals interparticle forces hold together fibrils into the actual fibre so that, when chrysotile breaks up, a large number of smaller fibres or fibrils are generated (Fubini & Otero Areán, 1999).

Amphiboles have an intrinsically elongated crystal structure which breaks up along planes within the crystal structure itself into progressively smaller fragments that generally retain a fibrous aspect. This structure can be described in terms of a basic structural unit formed by a double tetrahedral chain (corner-linked SiO_4 tetrahedra) of composition $(Si_4O_{11})_n^{6n-}$. These silicate double-chains share oxygen atoms with alternate layers of edge-sharing MO_6 octahedra, where M stands for a variety of cations: mostly Na^+, Mg^{2+}, Ca^{2+}, Fe^{2+}, or Fe^{3+} (Fubini & Otero Areán, 1999).

(b) Form and size

The pathogenic potential of asbestos depends upon its aspect ratio and fibre size. Fibre size affects respirability (respiratory zone falls off above aerodynamic diameters of 5 µm) and clearance by alveolar macrophages (section 4.1.1) (Donaldson & Tran, 2004). Short fibres are cleared more efficiently than longer ones, which undergo frustrated phagocytosis by macrophages. Short amosite fibres obtained by grinding long ones are less inflammogenic (Donaldson *et al.*, 1992), induce fewer chromosomal aberrations (Donaldson & Golyasnya, 1995), and reduce the inhibition of the pentose phosphate pathway (Riganti *et al.*, 2003). In-vitro genotoxicity studies demonstrated that both short and intermediate chrysotile asbestos fibres induced micronuclei formation and sister chromatid exchange in Chinese hamster lung cells. Intermediate fibres were more active than short fibres even when followed by treatment with dipalmitoyl lecithin, a principal constituent of pulmonary surfactant (Lu *et al.*, 1994). Long fibres but not short fibres of amosite asbestos, opsonized with rat immunoglobin, were shown to induce a dramatic enhancement of superoxide anions in macrophages isolated from rat lung (Hill *et al.*, 1995). Asbestos bodies are formed mostly on fibres longer than 20 µm (Roggli, 2004).

The role of the aspect ratio and size appears to be different for the three major asbestos-related diseases: i) asbestosis was reported as most closely associated with the surface area of retained fibres (NIOSH, 2009) although fibrosis also correlates with fibres > 2 µm long (Dodson *et al.*, 2003); ii) mesothelioma is better related to the numbers of fibres longer than about 5 µm and thinner than about 0.1 µm; and iii) lung cancer with fibres longer than about 10 µm and thicker than about 0.15 µm (NIOSH, 2009). Several studies, however, report the presence of very short fibres in lung and pleural tissue from patients with malignant mesothelioma (Dodson *et al.*, 2003; Dodson *et al.*, 2005; Suzuki *et al.*, 2005; Dodson *et al.*, 2007), suggesting caution to exclude short fibres (< 5 µm) in the development of asbestos-related diseases (Dodson *et al.*, 2003).

(c) Surface reactivity

In the last few decades, it has been accepted that, in addition to fibrous habit, surface reactivity also plays a role in the pathogenic effects of amphibole and chrysotile asbestos. The potential to release free radicals, among various other features, is considered the major determinant of the pathogenic response.

(i) Free-radical generation

Three different mechanisms of free-radical generation may take place at the surface of asbestos fibres, each one triggered by a different kind of active surface site: i) Fenton chemistry (yielding with H_2O_2 the generation of highly reactive hydroxyl radicals HO•); ii) Haber–Weiss cycle (in the absence of H_2O_2 and Fe(II), endogenous reductants allow progressive reduction of atmospheric oxygen to HO•); iii) homolytic

rupture of a carbon-hydrogen bond in biomolecules, with generation of carbon-centred radicals in the target molecule (peptides, proteins, etc.) (Hardy & Aust, 1995; Fubini & Otero Areán, 1999; Kamp & Weitzman, 1999).

Mechanism i) is relevant only in cellular compartments where H_2O_2 is present (i.e. phagolysosomal environment in macrophages), while Mechanisms ii) and iii)_may occur ubiquitously once fibres are inhaled. All mechanisms require the presence of iron ions. One stoichiometric chrysotile prepared by chemical synthesis, thus fully iron-free, was not active in free-radical generation (cell-free tests), did not induce lipid peroxidation, nor inhibit the pentose phosphate pathway in human lung epithelial cells, which is the opposite to what is found in natural specimens (Gazzano *et al.*, 2005). When loaded with less than 1 wt.% of Fe^{3+} the synthetic chrysotile also became active (Gazzano *et al.*, 2007). Asbestos fibres deprived of iron (following treatments with chelators) do not generate hydroxyl radicals (Fubini *et al.*, 1995) or damage DNA, and are less potent in causing lipid peroxidation *in vitro* (Hardy & Aust, 1995). However, not all iron ions are equally reactive in free-radical generation, depending upon their coordination and oxidation state (Shukla *et al.*, 2003; Bernstein *et al.*, 2005). Fe (II) is active even in trace amounts (Fubini *et al.*, 1995). Furthermore, Mechanism 3 requires isolated and poorly coordinated iron ions (Martra *et al.*, 2003; Turci *et al.*, 2007). The surface sites involved in this reaction are oxidized and become inactive following thermal treatments: amphibole asbestos fibres heated up to 400°C in air (Tomatis *et al.*, 2002) lose their potential in generating carboxyl radicals, but retain the reactivity for hydroxyl radicals, most likely through Mechanism 2, as long as their crystal structure is preserved. Conversely, the reduction of ferric into ferrous ions increases the radical activity (Gulumian *et al.*, 1993a). The radical yield appears unrelated to the total amount of iron (Gulumian *et al.*, 1993b), because chrysotile shows a similar behaviour to crocidolite in cell-free tests despite the lower content of iron (3–6% versus 27%). Iron oxides (magnetite, haematite) are unable to produce radical species, whereas model solids, e.g zeolites enriched with small amount of iron but with ions poorly coordinated and mostly in low valence state, are very reactive, particularly in hydrogen abstraction (Fubini *et al.*, 1995).

Iron-derived free radicals are believed to produce a variety of cell effects including lipid peroxidation (Ghio *et al.*, 1998; Gulumian, 1999), DNA oxidation (Aust & Eveleigh, 1999), TNF-release and cell apoptosis (Upadhyay & Kamp, 2003), adhesion (Churg *et al.*, 1998), and an increase of fibre uptake by epithelial cells (Hobson *et al.*, 1990).

(ii) Iron bioavailability and biodeposition

Iron can be removed from asbestos fibres by intracellular chelators. If iron is mobilized from low–molecular-weight chelators, e.g. citrate, redox activity may be altered. The chelator–iron complex can diffuse throughout the cell, and catalyse the formation of hydroxyl radicals. Mobilization of iron was shown to correlate with DNA strand breaks and with DNA oxidation induced by crocidolite, amosite, and chrysotile (Hardy & Aust, 1995). In human lung epithelial and pleural mesothelial cells, the extent of iron mobilization was also related to the inactivation of epidermal growth factor receptor (EGFR/ErbB1), a step in the pathway leading to apoptosis (Baldys & Aust, 2005).

Mineral fibres may also acquire iron which, under certain conditions, may modify their reactivity. Erionite (Dogan *et al.*, 2008) is able to bind both ferrous (through ion exchange) and ferric ions (through a precipitation or crystallization process). After ferrous-binding, erionite acquires the ability to generate hydroxyl radicals, and to catalyse DNA damage (DNA single-strand breaks); and after ferric-binding, the reactivity is acquired only in the presence of a reductant

(Hardy & Aust, 1995; Fach *et al.*, 2003; Ruda & Dutta, 2005). During their residence in the lung, asbestos fibres, like erionite fibres, acquire iron via a complex mechanism that may originate from the adsorption and disruption of ferritin, eventually yielding ferruginous bodies. These so-called asbestos bodies are preferentially formed onto long amphibole fibres but have also been found onto chrysotile fibres (Roggli, 2004). Although the presence of asbestos bodies in asbestos-related diseases is well documented, their biological role is still controversial. Iron deposition was thought to protect cells (Ghio *et al.*, 1997), but, deposited iron may become redox-active, thus enhancing the catalytic potential of the fibres (Ghio *et al.*, 2004). Asbestos bodies with amosite cores caused DNA single-strand breaks (Lund *et al.*, 1994); and increased radical damage to DNA was reported for ferritin-covered amosite in the presence of ascorbic acid (Otero-Areán *et al.*, 1999). Asbestos fibres might also disrupt normal iron homeostasis in the host by mobilizing and accumulating this metal (Ghio *et al.*, 2008).

Binding Fe (II) from solution increases iron mobilization from crocidolite by chelators, and induces DNA single-strand breaks. Increased lipid peroxidation and release of leukotriene B4 is found in alveolar macrophages from rats treated with Fe (III)-loaded crocidolite, and Fe (III)-loaded crocidolite fibres induce more DNA single-strand breaks *in vitro* than do untreated crocidolite fibres (Ghio *et al.*, 1992).

It was suggested that crocidolite stimulates inductible nitric oxide synthase by decreasing iron bioavailability (Aldieri *et al.*, 2001).

(d) Biopersistence, biodurability, and ecopersistence

The residence time in the lung depends upon both the clearance mechanisms and physico-chemical processes taking place. Clearance mechanisms are mainly related to the shape and size of the particle, whereas chemical composition, surface area, and structural parameters mainly affect leaching, dissolution, and breakage.

Selective leaching is more pronounced for serpentine asbestos than for amphiboles, which have no leachable "weak points" in their structure. Selective leaching of chrysotile occurs under strong acidic or chelating conditions, resulting in removal of Mg^{2+} ions. The kinetics vary according to the origin of the material, mechanical treatments, and associated contaminants, e.g. presence of nemalite (fibrous brucite) (Morgan, 1997). Chrysotile may lose magnesium *in vivo*, following phagocytosis by alveolar macrophages. The biological potential of magnesium-depleted chrysotile is greatly decreased (Langer & Nolan, 1994; Gulumian, 2005). Furthermore, leached fibres undergo breakage into shorter fibres, which may be cleared more readily from the lung. This accounts for the relatively low biopersistence of chrysotile compared to the amphiboles. The lungs of some chrysotile workers at autopsy contain low levels of chrysotile but substantial numbers of tremolite fibres, which is present in some chrysotile-bearing ores. For this reason, tremolite has been suggested to contribute to the carcinogenic effects seen in chrysotile miners (McDonald *et al.*, 1997; McDonald & McDonald, 1997; McDonald, 1998). Other asbestiform minerals may be associated with chrysotile, and, in some cases, modulate its toxicity, depending upon their amount and physicochemical characteristics. Balangeroite, occasionally intergrows with chrysotile (up to 5%) in the Balangero mine (Italy) and its sourroundings. Balangeroite fibres have a different structure from amphiboles, and are poorly eco- and bio-durable (Favero-Longo *et al.*, 2009; Turci *et al.*, 2009). Balangeroite may contribute to the overall toxicity of chrysotile, but it cannot be compared to tremolite nor considered to be solely responsible for the excess of mesothelioma found in Balangero (Mirabelli *et al.*, 2008).

In the natural environment, weathering processes carried out by micro-organisms

may induce chrysotile-leaching, contributing to its bioattenuation (Favero-Longo *et al.*, 2005). However, the dissolution of chrysotile is very low, because any breakdown of the silica framework takes place at a slow rate (Hume & Rimstidt, 1992), and is limited to a few layers in mild conditions (Gronow, 1987). Even in a strong acidic environment, the final product still retains a fibrous aspect at the nanoscale which is devoid of cations (Wypych *et al.*, 2005).

4.3.2 Direct genotoxicity

Mineral fibres may directly induce genotoxicity by catalysing the generation of reactive oxygen species resulting in oxidized DNA bases and DNA strand breaks that can produce gene mutations if not adequately repaired (IOM, 2006). Both asbestos and erionite fibres can induce DNA damage mediated by reactive oxygen species. Asbestos fibres have also been shown to physically interfere with the mitotic apparatus, which may result in aneuploidy or polyploidy, and specific chromosomal alterations characteristic of asbestos-related cancer (Jaurand, 1996).

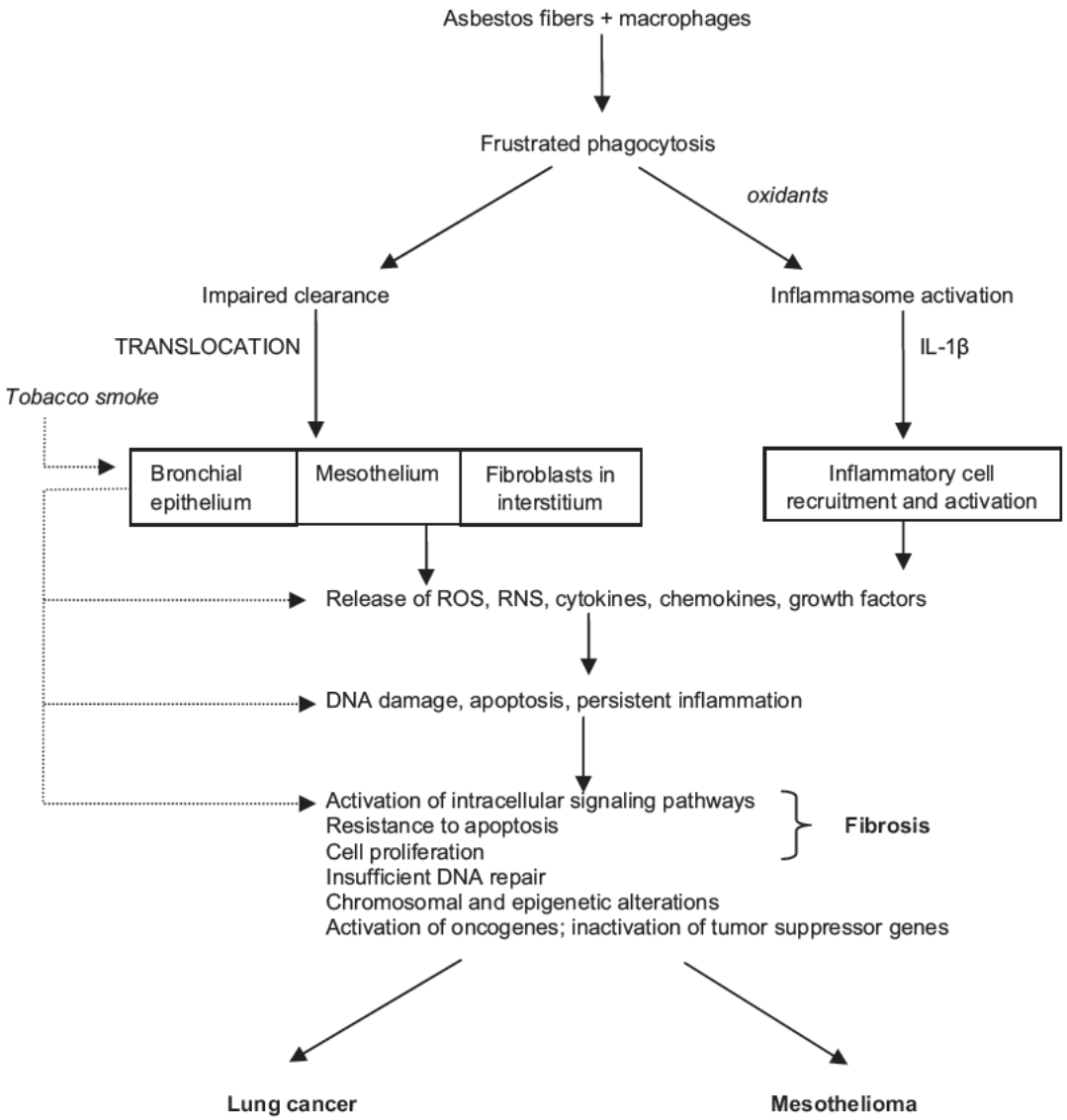
In addition to direct clastogenic and aneuploidogenic activities that may be induced following the translocation of asbestos fibres to target cell populations in the lungs, persistent inflammation and macrophage activation can secondarily generate additional reactive oxygen species, and reactive nitrogen species that can indirectly induce genotoxicity in addition to activation of intracellular signalling pathways, stimulation of cell proliferation and survival, and induction of epigenetic alterations (Fig. 4.2).

4.3.3 Indirect mechanisms

Asbestos fibres have unique and potent effects on alveolar macrophages that have been postulated to trigger the chain of events leading to chronic lung fibrosis (asbestosis), and lung cancer (Shukla *et al.*, 2003). Macrophages express a variety of cell-surface receptors that bind to mineral fibres leading to phagocytosis, macrophage apoptosis, or macrophage activation. Receptors expressed by macrophages and other target cells in the lung that bind mineral fibres include MARCO, a scavenger receptor class A, and integrin receptors (Boylan *et al.*, 1995; Gordon *et al.*, 2002; Arredouani *et al.*, 2005). Macrophage apoptosis has also been postulated to contribute to an increased incidence of autoimmune diseases in residents in Libby, Montana, USA, who are exposed to vermiculite contaminated with amphibole asbestos fibres (Noonan *et al.*, 2006; Blake *et al.*, 2008).

Phagocytosis of asbestos fibres leads to the excess generation of reactive oxygen and nitrogen species by both direct (described in Sections 4.3.1 and 4.3.2), and indirect mechanisms (Manning *et al.*, 2002). Alveolar macrophages phagocytize particulate materials and micro-organisms leading to assembly of NADPH oxidase in the phagolysosomal membrane that generates reactive oxygen species, which are potent antimicrobial agents. Asbestos fibres have elevated surface reactivity and redox-active iron that can generate hydroxyl radicals leading to lipid peroxidation, protein oxidation, and DNA damage resulting in lung injury that is amplified by persistent inflammation (Fig. 4.1 and 4.2). Recent investigations in genetically engineered mice have provided evidence for a key role of the NALP3 inflammasome as an intracellular sensor of the initial interactions between asbestos fibres and other crystals such as monosodium urate with macrophages (Yu & Finlay, 2008). The NALP3 inflammasome activates caspase-1 that cleaves IL-1β precursor to active IL-1β that is rapidly secreted (Cassel *et al.*, 2008; Dostert *et al.*, 2008). This cytokine then triggers the recruitment and activation of additional inflammatory cells and the release of additional cytokines including TNF-α, IL-6, and IL-8 that perpetuate a prolonged inflammatory response to these biopersistent mineral dusts (Shukla *et al.*, 2003).

Fig. 4.2 Proposed mechanism for the carcinogenicity of asbestos fibres



IL-1β, interleukin -1β; RNS, reactive nitrogen species; ROS, reactive oxygen species.
Adapted from Shukla *et al.* (2003), Kane (2006), Nymark *et al.* (2008)

The generation of reactive oxygen species by asbestos fibres has also been associated with inducing apoptosis in mesothelial cells (Broaddus *et al.*, 1996), and alveolar epithelial cells (Aljandali *et al.*, 2001).

Asbestos fibres have been shown to contribute to the transformation of a variety of target cells from different species *in vitro*, and to induce lung tumours and malignant pleural mesothelioma in rodents following chronic inhalation (Bernstein *et al.*, 2005). There are important species differences in the induction of asbestos-related cancers: rats are more susceptible to the induction of lung cancer, and hamsters are resistant to the induction of lung cancer but more susceptible to the development of malignant pleural mesothelioma (IARC, 2002). Subchronic inhalation studies using refractory ceramic fibres (RCF-1) suggest that the increased susceptibility of hamsters to developing malignant pleural mesothelioma may be related to greater translocation and accumulation of fibres in the pleural space, and an increased mesothelial cell proliferation in hamsters compared to rats (Gelzleichter *et al.*, 1999). There are serious limitations in extrapolating these species differences to humans. First, most human lung cancers, even in asbestos-exposed individuals, are confounded by tobacco smoke that has potent independent genotoxic effects as reviewed later in Section 4.4.1. Second, diffuse malignant mesothelioma in humans is usually diagnosed at an advanced stage, and there are no reliable premalignant changes or biomarkers that may provide clues about the molecular pathogenesis of mesothelioma associated with exposure to asbestos or erionite fibres (NIOSH, 2009).

A unifying mechanism based on the experimental in-vitro cellular and in-vivo rodent models is proposed in Fig. 4.2.

Recent biochemical studies have confirmed that oxidative damage to cytosine is a plausible biological mechanism leading to epigenetic alterations and development of cancer in association with persistent inflammation (Valinluck & Sowers, 2007). Neutrophils and macrophages are the source of reactive oxygen and nitrogen species triggered by phagocytosis of crystalline silica (quartz) or asbestos fibres. In addition, myeloperoxidase catalyses the formation of hypochlorous acid (HOC1) in neutrophils, and a specific peroxidase catalyses the formation of hypobromous acid (HOBr) in eosinophils (Babior, 2000). The formation of 8-oxoguanine, 5-hydroxymethylcytosine, or 5-hydroxycytosine interferes with DNA methylation and binding of methyl-CpG binding domains (MBDs). In contrast, chlorination or bromination of cytosine mimics 5-methylcytosine and induces heritable DNA methylation at previously unmethylated sites. Halogenated cytosines are also recognized by MBDs to facilitate chromatin remodelling. However, these modified bases are not recognized by DNA glycosylase, and are not repaired (Valinluck & Sowers, 2007).

This hypothesis linking heritable alterations in patterns of cytosine methylation with endogenous sources of oxidants released from inflammatory cells is a plausible explanation for the development of lung cancer and diffuse malignant mesothelioma associated with exposure to mineral fibres. Elevated neutrophils and eosinophils have been found in the pleural space following the inhalation of refractory ceramic fibres by hamsters and rats (Gelzleichter *et al.*, 1999). Furthermore, myeloperoxidase activity has been detected in rodent lungs following exposure to asbestos fibres, whereas a decreased lung inflammation was observed in asbestos-exposed myeloperoxidase-null mice (Haegens *et al.*, 2005). This indirect mechanism secondary to persistent inflammation may be responsible for altered epigenetic methylation profiles, which are characteristic of human malignant pleural mesotheliomas (Christensen *et al.*, 2009).

4.4 Susceptible populations

Both exogenous environmental and occupational exposures and endogenous factors including genetic susceptibility contribute to the development of lung cancer (NIOSH, 2009) and diffuse malignant mesothelioma (Weiner & Neragi-Miandoab, 2009). The best example of an exogenous exposure that is a major cofactor with asbestos fibres in the development of cancer of the larynx and of the lung is tobacco smoking (Table 4.3; Table 4.4; IARC, 2004; IOM, 2006). Additional environmental and occupational exposures are also risk factors for cancer of the larynx (Table 4.3) and of the lung (Table 4.4); these exposures are potential confounders in human epidemiological studies (IOM, 2006). Specific examples of these cofactors and other environmental and occupational exposures will be described in relationship to mechanisms of these cancers associated with mineral dust exposures.

4.4.1 *Other risk factors for cancer of the lung and of the larynx, and diffuse malignant mesothelioma*

(a) Tobacco smoke

Co-exposure to tobacco smoke and asbestos fibres is at least additive and possibly multiplicative in the development of lung cancer (Vainio & Boffetta, 1994). The inhalation of tobacco smoke (Walser *et al.*, 2008) as well as mineral fibres is associated with excess generation of reactive oxygen and nitrogen metabolites, cell injury and apoptosis, and persistent lung inflammation (Shukla *et al.*, 2003; IARC, 2004). Excess oxidant generation has been shown to enhance the penetration of asbestos fibres into respiratory epithelial cells, and to impair fibre clearance (McFadden *et al.*, 1986; Churg *et al.*, 1989), as well as altering the metabolism and detoxification of tobacco smoke carcinogens (Nymark *et al.*, 2008). Asbestos fibres can also adsorb tobacco smoke carcinogens and metals and facilitate their transport into the lungs (IOM, 2006). Asbestos fibres have also been shown to activate growth-factor receptors and cell-signalling pathways that stimulate cell proliferation and promote cell survival (Albrecht *et al.*, 2004). In summary, co-exposures to tobacco smoke and mineral fibres can amplify acquired genetic mutations induced by tobacco smoke carcinogens, and amplify cell proliferation in response to tissue injury leading to an increased risk for the development of cancer of the larynx and of the lung (Nymark *et al.*, 2008).

Table 4.3 Risk factors for the development of cancer of the larynx

Exposure	Reference
Active tobacco smoking	IARC (1986, 2004, 2012d)
Alcohol	IARC (1988, 2010, 2012d)
Mustard gas	IARC (1987a, 2012e)
Inorganic acid mists containing sulfuric acid	IARC (1992, 2012e)
Asbestos fibres	IOM (2006), IARC (2012b)
Human papilloma virus (HPV): types 6, 11, 16, 18 limited evidence	IARC (2007, 2012c)

Compiled by the Working Group

(b) Other occupational and environmental exposures

Alcohol and occupational exposure to irritants (Table 4.3) also contribute to the development of cancer of the larynx. These irritants, similar to inhalation of tobacco smoke, can cause repeated episodes of injury to the respiratory epithelium, resulting in metaplasia and dysplasia (Olshan, 2006); these preneoplastic lesions may then acquire additional molecular alterations and progress towards the development of invasive lung or laryngeal carcinoma. Other occupational exposures responsible for the development of lung cancer include direct-acting carcinogens such as ionizing radiation (IARC, 2000, 2012a), and metals (reviewed in IARC, 2012b).

Table 4.4 Risk factors for the development of cancer of the lung

Exposure	Reference
Active and passive tobacco smoking	IARC (2004, 2012d)
Ionizing radiation	IARC (2000, 2012a)
Respirable dusts and fibres:	
Asbestos	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Crystalline silica (quartz)	IARC (1997, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), McDonald *et al.* (2004), IARC (2012b)
Bis(chloromethyl)ether and chloromethyl methyl ether	IARC (1987a, 2012e)
Arsenic and arsenic compounds	IARC (1987a, 2012b)
Beryllium	IARC (1993, 2012b)
Cadmium and cadmium compounds	IARC (1993, 2012b)
Hexavalent chromium	IARC (1990, 2012b)
Nickel sulfate, oxides, and sulfides	IARC (1990, 2012b)
Soots	IARC (1985, 1987a, 2012e)

Compiled by the Working Group

The strongest risk factors associated with the development of diffuse malignant mesothelioma include environmental or occupational exposures to erionite, asbestos fibres, and talc or vermiculite contaminated with asbestos fibres (Table 4.5; NIOSH, 2009). It is unknown whether the carcinogenic effects of exposure to mixed dusts contaminated with asbestos fibres can be entirely attributed to the asbestos fibres or whether co-exposure to talc or vermiculite dusts potentiates the retention and/or biological activity of asbestos fibres *in vivo* (Davis, 1996). The occurrence of talc pneumoconiosis and its relationship to other mineral dust contaminants including quartz and tremolite was recently reviewed (IARC, 2010). In-vitro assays of talc cytotoxicity were also summarized (IARC, 2010). No experimental studies have been published assessing the cytotoxicity of vermiculite contaminated with asbestos fibres. A sample of the mixture of amphibole fibres associated with Libby vermiculite ore has been shown to induce cytotoxicity and oxidative stress in macrophages *in vitro* (Blake *et al.*, 2007).

(c) *SV40 and HPV viruses*

Two human DNA tumour viruses have been linked with an increased risk for cancer of the larynx (Table 4.3; high-risk subtypes of human papillomavirus (HPV)) and diffuse malignant mesothelioma (Table 4.5; Simian virus 40 (SV40)).

The evidence for HPV 16 in the development of cancer of the larynx has been evaluated as limited, although it has been implicated as an independent risk factor in the development of other squamous cell carcinomas arising in the head and neck region (IARC, 2007, 2012c).

The association between exposure to SV40 and asbestos fibres in the development of diffuse malignant mesothelioma is highly controversial (Butel & Lednicky, 1999; Gazdar *et al.*, 2002; Shah, 2004; IOM, 2006). SV40 is not an essential cofactor for the development of mesothelioma; for example, residents of the Cappadocian villages in Turkey have a very high risk for diffuse malignant mesothelioma but do not have evidence of SV40 exposure (Dogan *et al.*, 2006). Although there are several in-vitro mechanistic

Table 4.5 Risk factors for the development of diffuse malignant mesothelioma

Exposure	Reference
Asbestos fibres	IARC (1987a, 2012b)
Erionite	IARC (1987a, 2012b)
Talc containing asbestiform fibres	IARC (1987a, 2012b)
Vermiculite contaminated with asbestos fibres	Amandus & Wheeler (1987), IARC (1987a, 2012e), McDonald *et al.* (2004)
Thorotrast	IARC (2001, 2012a)

Compiled by the Working Group

studies that support a role for SV40 viral oncogenes in the transformation of mesothelial cells, the human epidemiological evidence is inconclusive to support a causal association (Weiner & Neragi-Miandoab, 2009).

4.4.2 Genetic susceptibility

(a) Cancer of the lung

Tobacco smoke is the major cause of cancer of the lung; however, only a few rare hereditary syndromes are associated with an increased risk of lung, as well as other cancers: Bloom syndrome, Li-Fraumeni syndrome, and hereditary retinoblastoma (Lindor *et al.*, 2006). Other genetic polymorphisms in genes related to the metabolism and detoxification of tobacco smoke carcinogens, antioxidant defenses, and DNA repair have been suggested as predisposing factors for the development of lung cancer, although individually they contribute minimally to an increased risk (IOM, 2006). Attempts have been made to identify genetic polymorphisms in enzymes involved in xenobiotic metabolism and antioxidant defense that increase the risk for asbestos-related lung cancer; however, no consistent associations have been found (Nymark *et al.*, 2008).

(b) Diffuse malignant mesothelioma

With the exception of certain populations who have been exposed environmentally to asbestos or erionite fibres since birth (NIOSH, 2009), the development of diffuse malignant mesothelioma even in occupationally exposed workers is less common than the development of lung cancer (Nymark *et al.*, 2008). This observation has led to the hypothesis that there may be a genetic predisposition to the development of diffuse malignant mesothelioma following exposure to asbestos or erionite fibres. Isolated case reports provide examples of diffuse malignant mesothelioma in patients with neurofibromatosis type 2 (Baser *et al.*, 2002) or Li-Fraumeni syndrome (Heineman *et al.*, 1996) who are also exposed to asbestos. Several reports of familial cases of diffuse malignant mesothelioma are complicated by a common household exposure history (Weiner & Neragi-Miandoab, 2009). The strongest association between environmental exposure to erionite and genetic susceptibility to diffuse malignant mesothelioma has been provided by pedigree analysis of residents in the Cappadocia region of Turkey (Dogan *et al.*, 2006). However, there is skepticism about the accuracy of this analysis, and a recent review indicated that familial clusters can account for only 1.4% of cases of mesothelioma in Italy between 1978–2005 (Ascoli *et al.*, 2007; Ugolini *et al.*, 2008). One study has reported an association between genetic polymorphisms in the X-ray complementing group 1 gene (XRCC1) and the development of malignant mesothelioma in a population exposed to asbestos fibres (Dianzani *et al.*, 2006). More sensitive genome-wide association studies may uncover new markers for genetic susceptibility that predict increase risks of developing diffuse malignant mesothelioma following exposure to asbestos or erionite fibres.

4.5 Synthesis

The mechanistic basis for asbestos carcinogenicity is a complex interaction between crystalline mineral fibres and target cells *in vivo*. The most important physicochemical properties of asbestos fibres related to pathogenicity are surface chemistry and reactivity, surface area, fibre dimensions, and biopersistence. Multiple direct and indirect mechanisms have been proposed based on numerous in-vitro cellular assays, and acute and subchronic animal bioassays. These complex mechanisms most likely interact at multiple stages during the development of lung cancer and diffuse malignant mesothelioma.

The following general mechanisms have been proposed for the carcinogenicity of asbestos fibres (Fig. 4.1; Fig. 4.2):

1. Direct interaction between asbestos fibres and target cells *in vitro*:
   - Asbestos and erionite fibres have been shown to generate free radicals that directly induce genotoxicity as assessed by DNA breaks and oxidized bases in DNA.
   - Asbestos fibres have also been shown to interfere with the mitotic apparatus by direct physical interaction resulting in aneuploidy and polyploidy.
2. Indirect mechanisms:
   - In laboratory animals, asbestos fibres have been shown to induce macrophage activation and persistent inflammation that generate reactive oxygen and nitrogen species contributing to tissue injury, genotoxicity, and epigenetic alterations. Persistent inflammation and chronic oxidative stress have been associated with the activation of intracellular signalling pathways, resistance to apoptosis, and stimulation of cell proliferation.

There are significant species differences in the responses of the respiratory tract to the inhalation of asbestos fibres. The biological mechanisms responsible for these species differences are unknown. Based on comparative animal experimental studies, there may be differences in deposition and clearance of fibres in the lungs, in severity of fibrosis, in kinetics of translocation of fibres to the pleura, and in levels or types of antioxidant defense mechanisms.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite). Asbestos causes mesothelioma and cancer of the lung, larynx, and ovary. Also positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. For cancer of the colorectum, the Working Group was evenly divided as to whether the evidence was strong enough to warrant classification as *sufficient*.

There is *sufficient evidence* in experimental animals for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite).

All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) are *carcinogenic to humans (Group 1)*.

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Exhibit 8

Using the geologic setting of talc deposits as an indicator of amphibole asbestos content

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Abstract This study examined commercial talc deposits in the U.S. and their amphibole-asbestos content. The study found that the talc-forming environment directly influenced the amphibole and amphibole-asbestos content of the talc deposit. Large talc districts in the U.S. have mined hydrothermal talcs that replaced dolostone. Hydrothermal talcs, created by siliceous fluids heated by magmas at depth, consistently lack amphiboles as accessory minerals. In contrast, mineable talc deposits that formed by contact or regional metamorphism consistently contain amphiboles, locally as asbestiform varieties. Examples of contact metamorphic deposits occur in Death Valley, California; these talc-tremolite deposits contain accessory amphibole-asbestos. Talc bodies formed by regional metamorphism always contain amphiboles, which display a variety of compositions and habits, including asbestiform. Some industrial mineral deposits are under scrutiny as potential sources of accessory asbestos minerals. Recognizing consistent relations between the talc-forming environment and amphibole-asbestos content may be used in prioritizing remediation or monitoring of abandoned and active talc mines.

Keywords Talc · Amphibole-asbestos · Geologic setting · Hydrothermal · Metamorphic · USA

Introduction

The presence of amphibole asbestos as minor accessory minerals in some talc deposits, and its potential health impacts on the human respiratory system, have been the focus of considerable research and contentious debate for at least 30 years (Goodwin 1974; Occupational and Safety and Health Administration 1992). Talc-asbestos issues have drawn renewed attention, such as news reports in 2000 contending that the fibrous talc used to add strength to the best-selling brands of children's crayons contained amphibole asbestos (Beard and others 2001). To investigate the extent and character of amphibole minerals in talc deposits, a group at the U.S. Geological Survey (USGS) is examining the relationships between amphiboles and talc in U.S. deposits. This study, involving field examinations and sampling, laboratory analyses, and an extensive literature review, has revealed that a consistent relationship occurs within large (commercial) and small U.S talc deposits—that is, the primary talc-forming environment directly controlled the ultimate amphibole content of the talc deposit.

Talc deposits are the products of metasomatism caused by regional metamorphism, contact metamorphism, or hydrothermal processes (meteoric fluids or brines heated by distant or buried intrusions). Two of these talc-forming mechanisms—contact metamorphism and hydrothermal processes—are well represented by large, historically mined deposits in the Death Valley region of southern California. Results of field and laboratory studies on these Death Valley deposits, described herein, reflect the consistent associations of amphibole-rich talc deposits with contact metamorphism versus amphibole-poor talc with hydrothermal processes.

A number of U.S. talc deposits of commercial size (under past or present economic conditions) were formed by metasomatic processes driven by regional metamorphism; these large bodies consistently contain talc intergrown with amphiboles, such as tremolite and (or) anthophyllite. Debate over the asbestos mineral content (major versus trace amounts) within these talc-amphibole deposits is the result of differing interpretations of the predominant habit (asbestiform versus non-asbestiform) of the amphibole particles. The complicating factors that face analysts examining this type of talc ore material are discussed.

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Asbestos

Asbestos is a commercial-industrial term with a long history, and is not a mineralogical definition. "Asbestos" in the

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latter half of the 20th century became widely used in regulatory language to refer to well developed, long, thin particles (fibers or fibrils) and fiber bundles of specific mineral compositions, which have fulfilled particular industrial applications. In the U.S., asbestos is most commonly defined as the asbestiform variety of 6 naturally occurring hydrated silicate minerals; these include chrysotile, the asbestiform member of the serpentine group, and five minerals of the amphibole group: the asbestiform varieties of (1) riebeckite (commercially called crocidolite), (2) cummingtonite-grunerite (commercially called amosite), (3) anthophyllite (anthophyllite asbestos), (4) actinolite (actinolite asbestos), and (5) tremolite (tremolite asbestos) (Occupational Safety and Health Administration 1992). The qualities of asbestos that make it useful and desirable for commercial use are its high tensile strength, flexibility, and its resistance to heat, chemicals, and electricity.

The inherent properties of asbestos—fibers that are durable, long, and thin—appear to contribute to the toxicity of these mineral particles when lodged inside the human respiratory system (Stanton and others 1981; Wylie and others 1993). Occupational exposures to asbestos have been linked to asbestosis (scarring of the lungs, "pulmonary interstitial fibrosis"), lung cancer, and malignant mesothelioma (tumor development within the pleural membrane lining the chest cavity and (or) in the peritoneum lining the abdominal and pelvic walls and their viscera) (Skinner and others 1988; Mossman and others 1990; Guthrie and Mossman 1993; Nolan and others 2001). Historically, chrysotile has accounted for more than 90% of the world's asbestos production, and presently over 99% of the world production (Ross and Virta 2001; Virta 2001, 2002). Whereas mining, processing, and use of chrysotile has been much more common, several studies suggest that amphibole asbestos, even when occurring as a minor accessory in chrysotile deposits, may be the primary cause of mesothelioma in asbestos-related occupations (Ross 1981, 1984, 2001; Mossman and others 1990; Browne and Wagner 2001; Gibbs 2001; Langer 2001; Pooley 2001a, 2001b). As noted by Mossman and others (1990, p. 296): "The persistence of amphiboles in human lungs may be attributed to their increased ability to penetrate the peripheral lung, lack of clearance, or durability". Wagner and others (1960) described the high rates of malignant mesothelioma in workers and nearby residents of crocidolite (asbestiform riebeckite) mines in the Cape Province of South Africa. Following publication of that study in 1960, mesothelioma became increasingly recognized as an occupational risk in the mining, milling, and handling of rocks that contain amphibole asbestos and their by-products.

In recent years, there has been a renewed focus upon the hazards related to inhalation of amphibole asbestos; in particular, exposures due to the mining and processing of some amphibole-bearing industrial mineral deposits, as well as environmental exposures to amphibole-rich bedrock, such as road cuts and excavations that expose asbestos-bearing rock (Browne and Wagner 2001). For example, unusually high incidences of asbestos-related mortality and respiratory disease in the small town of Libby, Montana, have been attributed to amphibole mineral fibers intergrown with the vermiculite deposits mined and milled near the town from 1923 to 1990 (U.S. Senate Committee on Environment and Public Works 2000; Dearwent and others 2000). The California Division of Mines and Geology has mapped outcrops of ultramafic rocks in California to indicate country rocks with the potential to host chrysotile and actinolite-series asbestos (Churchill and Hill 2000). Other examples of occupational and environmental exposures to asbestos are described in Nolan and others (2001).

The history and study of naturally occurring asbestos, its associated health impacts, and the multiple, complex issues that revolve around asbestos are discussed in Campbell and others (1977), Ross (1981), Zoltai (1981), Levadie (1984), Skinner and others (1988), Mossman and others (1990), Occupational Safety and Health Administration (1992), Guthrie and Mossman (1993), Nolan and others (2001), and Virta (2001, 2002). Current federal regulations are provided in the Code of Federal Regulations (CFR), including regulations on occupational exposures to asbestos excepting construction and ship-related work (CFR 29, part 1910.1001); CFR regulations are updated as needed on July 1.

Exploitable talc deposits and amphiboles

Talc is a hydrous silicate with an idealized composition of $Mg_3Si_4O_{10}(OH)_2$, but can contain major amounts of Fe, minor Al and F, and trace Mn, Ti, Cr, Ni, Ca, Na, and K (Evans and Guggenheim 1988; Greenwood 1998). Significant talc deposits occur in the U.S. in the Appalachians, from Vermont to Alabama, in the West in Montana, California, Nevada, Washington, Idaho, and New Mexico (Piniazkiewicz and others 1994). Large deposits also occur in Texas, and small soapstone mines once operated in Arkansas, but economic deposits are otherwise lacking between the Appalachians and the Rocky Mountains. Commercial talc deposits have replaced two general rock types: (1) Dolostone (dolomite or dolomitic marble), which were selectively replaced by reactions with large volumes of heated waters carrying silica in solution, mobilized by magmatic or metamorphic mechanisms. The dolostone-hosted replacement deposits range from cm-thick pods to the 29-m-thick talc body at the Treasure Chest mine near Dillon, Montana (Berg 1979). Today and in the past, the largest talc producing districts in the U.S. exploited talc deposits replacing dolostone, and to a lesser extent, magnesite. (2) The second common talc hosts are ultramafic rocks, mainly dunites and peridotites, altered by metasomatism through contact or regional metamorphism. Magnesium silicates in these rocks reacted with SiO_2-saturated aqueous pore fluids during metamorphism to form nearly monomineralogic bodies of talc adjacent to zoned sequences of talc-carbonate-, calcic amphibole-chlorite-, and chlorite-dominant zones in addition to complexly mixed zones (described by Sanford 1982). These deposits

form rinds on the ultramafic bodies or nearly replace them; they are typically tabular or lenticular talc bodies that can reach 100 m in thickness and extend more than 300 m in length. Large deposits of this type are mined in Vermont, and smaller deposits have been mined in other eastern states, California, and Texas. The ultramafic-hosted deposits have been equally important sources of pure talc and darker talc (soapstone), the dark talcose bodies owing their coloration to amphibole, serpentine, and chlorite impurities (Piniazkiewicz and others 1994).

The host rock composition and process of formation determines the qualities of talc, which in turn affects the industrial applications of a particular deposit. The grain size and shape, color, and purity of talc influence its uses (Piniazkiewicz and others 1994). In addition, the talc-forming mechanism—hydrothermal processes, contact metamorphism, or regional metamorphism—directly influenced the ultimate amphibole content of the talc ore body, described below through examples. Within a single mineral deposit, such as some talc ore bodies, amphibole crystals may range in habit from blocky to prismatic to acicular to asbestiform. In describing amphibole asbestos, Wylie (2000, p. 56) notes that: "Amphibole-asbestos fibrils range in width from about 1 to 0.01 μm" and "individual fibrils and bundles of fibrils may attain lengths of hundreds to thousands of times their widths".

Study methods

Samples of talc ore material were collected at several mine sites, which are described below. Each sample was collected as a composite, containing at least 30 pieces of randomly selected talcose rock at each particular sample spot. The samples are intended to represent the talcose material mined at each site, collected mainly from mines that are inactive and abandoned, excepting those samples collected from an active open pit of the Yellowstone mine, southwest Montana.

Dust coating the inside of the plastic sampling bag was examined using a JEOL 5800-LV scanning electron microscope (SEM), equipped with an Oxford ISIS energy-dispersive system (EDS) with ultra-thin window detector. The EDS provided semi-quantitative chemical data that was reduced using the Oxford ISIS standardless software with the ZAF correction procedure selected. Analyses were performed on single, isolated structures, not on fibers that lay across other mineral particles. The operating conditions of the instrument were 15 kV, 0.5–3 nA (cup), and approximately 30% dead time. These conditions would excite an analysis volume of ~2 μm.

The matrix corrections used do not account for particle geometry. However, Small and Armstrong (2000) demonstrated that at 10–15 kV (utilized by this study) geometry-induced errors in the analyses of particles can be relatively small. One of the amphibole-rich study samples was analyzed by EDS and by electron probe microanalysis with wavelength dispersive spectroscopy (WDS) to evaluate the accuracy of the EDS measurements. Table 1 shows the comparison of analytical results by EDS and WDS. The amphibole nomenclature used in this study follows the recommendations of Leake and others (1997).

Samples for x-ray diffraction (XRD) analyses were pulverized and mechanically split. The minerals identified by XRD in the samples were categorized as major, minor, and trace mineral constituents of the analyzed split. "Major" minerals are estimated to comprise >25 wt% of the sample, "minor" minerals form 5–25 wt% of the sample, and "trace" minerals form <5 wt% of the sample. These estimates were based on the experience of the XRD operator with his instrumentation and its data output. The pulverized splits examined by this study provide snapshots of the mineralogy and variability in the talcose ores. However, quantitative estimates of the talc or amphibole content should not be interpreted from the XRD results shown in this report.

The XRD technique can identify the amphibole minerals within a sample as members of the tremolite-actinolite-ferroactinolite series, but is not able to determine the specific amphibole species. It is also not possible to positively distinguish between tremolite and the sodic-calcic amphiboles winchite and richterite by XRD.

Table 1
Comparison of the analyses of tremolite particles in one tremolite-rich specimen from the Death Valley region, as measured by two techniques: (1) energy dispersive x-ray analysis (EDS) on polished and single unpolished grains, and (2) electron probe microanalysis with wavelength dispersive spectroscopy (WDS) on polished grains. Data are expressed in cation proportions, which were calculated by stoichiometry using 23 oxygen atoms

Mount type	Particle L x W (μm)	Analysis method	K	Na	Ca	Mn	Fe	Mg	Ti	Al	Si
Polished	203×106	WDS	0.01	0.06	1.88	0.01	0.04	4.93	bdl	0.03	7.99
		EDS	bdl	bdl	1.7	bdl	0.1	4.9	bdl	bdl	8.1
Polished	362×226	WDS	0.01	0.06	1.88	0.01	0.05	4.94	bdl	0.03	7.97
		EDS	bdl	bdl	1.7	bdl	bdl	5.0	bdl	bdl	8.1
Polished	620×228	WDS	0.01	0.06	1.87	0.02	0.06	4.90	bdl	0.03	8.00
		EDS	bdl	bdl	1.7	bdl	0.1	5.0	bdl	bdl	8.1
Polished	241×28.8	WDS	0.01	0.05	1.88	0.02	0.06	4.94	bdl	0.03	7.99
		EDS	bdl	bdl	1.8	bdl	bdl	4.9	bdl	bdl	8.1
Polished	140×14.3	WDS	0.01	0.05	1.85	0.02	0.06	4.93	bdl	0.04	8.00
		EDS	bdl	bdl	1.8	bdl	0.1	5.0	bdl	bdl	8.1
Loose	225×170	EDS	bdl	bdl	1.8	bdl	0.1	4.9	bdl	bdl	8.1
Loose	445×166	EDS	bdl	bdl	1.8	bdl	0.1	4.8	bdl	bdl	8.1
Loose	104×27.1	EDS	bdl	bdl	1.7	bdl	0.1	5.0	bdl	bdl	8.1
Loose	20.2×3.4	EDS	bdl	bdl	1.7	bdl	0.1	5.1	bdl	0.1	8.0
Loose	18.5×0.9	EDS	bdl	bdl	1.8	0.1	0.1	5.2	bdl	bdl	7.9
Loose	5.8×0.8	EDS	bdl	bdl	1.7	0.1	0.2	5.1	bdl	0.1	7.9
Loose	6.7×1.1	EDS	bdl	bdl	1.9	bdl	0.1	5.3	bdl	bdl	7.8
Loose	3.9×1.5	EDS	bdl	bdl	1.8	bdl	bdl	5.0	bdl	0.1	8.0
Loose	13.4×1.0	EDS	bdl	bdl	1.8	0.1	0.1	5.1	bdl	0.2	7.9

bdl, below the detection limit of the analytical technique

Amphibole-poor talc deposits formed by hydrothermal processes

Geologic environments that host hydrothermal talc deposits

The term "hydrothermal" is commonly used in a general sense to describe the actions and products of hot fluids, often, but not always, implying an association with igneous processes. In this discussion, hydrothermal talc refers to deposits thought to be the products of fluids heated by a distant magma source, usually at depth. For example, in the Talc City district, California, no evidence of contact or regional metamorphism is apparent in the host or country rocks; the source of the heat that drove the talc-forming process is not obvious, and has been attributed to buried or distant igneous intrusions. Heat sources for the southwest Montana talc event(s) are speculated to be sills that intruded an overlying Proterozoic basin, heating and circulating basin brines towards underlying Archean marbles. Thus, "hydrothermal talc" refers to talc ore bodies that are not directly associated with regional metamorphism and are not found directly against an igneous intrusion.

The large, amphibole-poor, hydrothermal talc deposits of southwest Montana, Talc City, California, and west Texas, as examples, may represent the products of saline, siliceous fluids mobilized by basin-scale or localized magmatic activity. This genetic association is supported by the recent fluid-inclusion study by Gammons and Matt (2002) of the hydrothermal talc deposit currently excavated at the Yellowstone mine, southwest Montana, which indicated the presence of highly saline fluids during the talc formation. They proposed that "high heat flow, enhanced by injection of thick sills into the (Proterozoic) sedimentary pile, forced connate brines out of the bottom of the (Proterozoic) Basin and into the underlying or adjacent Precambrian basement, where they caused retrograde metamorphism and formation of economic talc and chlorite deposits" (replacing dolomitic marble and quartzo-feldspathic gneiss, respectively) (Gammons and Matt 2002, p. 44).

Talc City district, California

The historical significance of the Talc City mining district in California from World War I through the 1940s is well documented by Page (1951). The district is in the Talc City Hills about 47 km southeast of Lone Pine, California. Page visited and sampled the district during its peak of production in the mid 1940s; the reader is referred to his report (Page 1951) for descriptions of the district's geology, talc deposits, and mines. Gay and Wright (1954) completed a geologic map of the Talc City area.

The talc deposits of the Talc City district are thick lenses and irregular masses hosted mainly by dolomite. To a much lesser extent talc bodies occur in "silica rock", named by Page (1951) for an unstratified, massive rock composed mostly of interlocking quartz; it resembles quartzite in outcrop. Limestone is also nearby. Bedded dolomite is altered to massive dolomite adjacent to the talc deposits; both are often closely associated with silica rock. The silica rock is discontinuous at the mine sites, forming isolated lenses surrounded by massive dolomite. Silica rock appears to be partially replaced by talc at some of the deposits. Petrographic examination of the silica rock reveals microscopic patches of talc in interstitial areas between quartz grains (Page 1951).

Granitic bodies crop out from about 0.8 to 3.2 km distance from the mines. The granitic rocks locally have been hydrothermally altered, suggesting they were affected by the talc-forming hydrothermal event(s) and were not the source of fluids. Dikes ranging in composition from basalt to diorite to felsite crop out near the Talc City and Frisco mines (Page 1951). These dikes are also hydrothermally altered and interpreted to predate the talc alteration (Page 1951). A magmatic source of hydrothermal fluids is not obvious within the district. If buried, it may be best viewed by geophysical methods.

Page (1951) proposed a model for talc formation in the Talc City area that involved the following events:

1. The area was originally covered by mostly limestone, with lesser interbeds of dolomite, shale, and sandstone;
2. Hydrothermal fluids rich in Mg rose through and fractured the overlying limestones and altered them into massive dolomite, perhaps also converting sandstones to the "silica rock";
3. A second event of fracturing accompanied another influx of hydrothermal waters enriched in Si and Mg, which replaced massive dolomite with large talc deposits and replaced silica rock with talc lenses. Page (1951) suggested the talc formed by the addition of silica and water to dolomite, and the addition of silica, water, and Mg to silica rock. This general reaction, shown below, is commonly invoked to explain the replacement of dolomite by talc:

$$3\ \text{dolomite} + 4SiO_{2(aq)} + 1H_2O = 1\ \text{talc} + 3\ \text{calcite} + 3CO_2$$

Abundant fracturing and shearing of country rocks in the district suggest that fracture systems controlled and aided fluid flow and talc formation. Page's interpretations are based on field relationships. However, by general

appearances, the talc deposits and associated rocks of the Talc City district do not display features typical of regional metamorphic processes, such as prominent foliation or compression structures.

The study sampled talc ore from pits or dumps at five sites in the Talc City district (Tables 2 and 3). No evidence of amphibole minerals was found in ore samples from this district based on x-ray diffraction (Table 2) and SEM-EDS analyses of the samples. Platy talc is mixed with small amounts of calcite, clinochlore, dolomite, quartz, kaolinite, vermiculite (uncertain identification) and K-feldspar (listed left to right in decreasing abundance). A friable white layer interlayered with the talc ore body at the Frisco mine consists of mostly quartz with accessory plagioclase, muscovite, dolomite, talc, and kaolinite. Thus, none of the descriptions of Page (1951), nor the results of our sampling and mineralogical analyses, indicate the presence of amphiboles in the talc deposits of the Talc City district.

Yellowstone mine, southwest Montana

The Yellowstone talc mine is on the northeast flank of the Gravelly Range near Ennis, Montana. This enormous talc body (greater than 5.5 million short tons of known reserves) is the largest known in southwestern Montana, a region that contains a total of 57 talc mines, talc prospects, and known talc occurrences (Berg 1979; Van Gosen and others 1998). The Yellowstone mine is the largest talc-producer in the U.S., and two other large talc mines, the Regal and Treasure State mines, currently operate farther to the west in the Ruby Range. All three mines are open-pit operations.

All of the economically important talc deposits in the Ruby and Gravelly Range region of southwest Montana replaced dolomitic marbles of Archean age. In much smaller amounts, talc also replaced magnesite, quartz, tremolite, serpentine, and calcite, which are accessory constituents of the host marble (Berg 1979). Talc occurrences range from veinlets and pods centimeters thick up to huge masses, such as the thick talc body at the Yellowstone mine, which is at least 30 m thick (bottom not yet found). Most of the southwest Montana talc bodies are lenticular and elongate, and in most places, talc lenses are parallel to the lithologic layering of the marble. However, talc bodies cut across layering at the Yellowstone mine (Cerino 2002).

The origin of the southwest Montana talc deposits is not completely understood, but recent work has reaffirmed earlier observations that the talc bodies appear to have formed during the Precambrian because they are restricted to Archean dolomitic marbles and do not replace overlying Cambrian dolomites. This observation was supported by a published age of 1.36 Ga by the $^{40}Ar/^{39}Ar$ method for muscovite intergrown with talc in the Ruby Range (Brady and others 2003). A recent fluid inclusion study of the Yellowstone mine deposits (Gammons and Matt 2002, p. 44) determined that "the fluids responsible for talc formation were saline brines (roughly 7x saltier than modern seawater), and were enriched in $CaCl_2$". They calculated burial depths during talc formation of more than 3 km at formation temperatures of 190 to 250 °C. Their model for talc formation at the Yellowstone mine site involves saline fluids that descended along growth faults in an overlying Proterozoic basin that may have existed above the Archean dolomitic marbles at about 1.36 Ga; they suggested the saline fluids were either supplied by connate brines in the basin sediments or by overlying seawater. Their model, as well as earlier models for talc formation in southwest Montana (Olson 1976; Anderson and others 1990; Brady and others 2003), invoke very large water to rock ratios to form these deposits, through the general reaction:

$$3\,\text{dolomite} + 4SiO_{2(aq)} + 4H_2O = 1\,\text{talc} + 3Ca^{2+} + 6HCO_3^-$$

Anderson and others (1990) suggested that water to rock ratios of more than 600 are required by this reaction to carry sufficient silica in solution and flush most of the calcite out of the system.

Regardless of the source of the hydrothermal fluids or the circulation mechanism, the end result at the Yellowstone mine site is large bodies of mainly massive talc with light green coloration, which contains trace amounts of limonite and goethite that replaced pyrite, along with traces of graphite. The light green color is attributed to 1% Fe^{2+} substituting for Mg in octahedral sites within the talc lattice (Cerino 2002). Minor substitution of F^- for OH^- is also noted. The bulk chemical compositions of talcose ores are shown in Table 3.

This study analyzed four samples of massive pale-green talc ore collected by the lead author from the floor of two open pits of the Yellowstone mine—two samples from an active pit and two from an inactive pit. XRD and SEM-EDS analyses of these samples revealed talc, with no other mineral impurities found. Late-stage (post-talc), large euhedral crystals of quartz and dolomite, accompanied by fine-grained Fe oxide minerals, commonly line cavities developed along faults that cut the talc bodies and country rock. These faults, which display normal displacements, are interpreted as growth faults (Cerino 2002) with intermittent movement through time. Magnesite is plentiful in the dolomitic marble that borders the talc deposits.

Table 2
Mineral abundances in samples of hydrothermal talc ore collected from abandoned talc mines in the Talc City district near Lone Pine, California. The latitude and longitude values were measured by GPS using the North American Datum of 1927, CONUS. In regard to the x-ray diffraction results (see text), "major" minerals are estimated to comprise >25 wt% of the sample analyzed; "minor" minerals form 5–25 wt%; and "trace" minerals comprise <5 wt%

Site name, sample number	Latitude, longitude	Minerals identified by x-ray diffraction		
		Major	Minor	Trace
Talc City mine	36.3315, -117.6677			
11ADV02		Talc		Quartz, clinochlore
11CDV03		Talc	Clinochlore, vermiculite(?)	Quartz, calcite
11FDV03		Talc		Kaolinite
12ADV02		Talc, calcite		Dolomite, kaolinite
Silver Dollar mine	36.3371, -117.6617			
13ADV02		Calcite, talc	Clinochlore	Quartz, dolomite
Alliance mine	36.3421, -117.6717			
14ADV02		Talc		Quartz
14DDV03		Talc, quartz		Vermiculite(?), kaolinite
Frisco mine	36.3303, -117.6800			
15ADV02		Clinochlore		Talc, K-feldspar
Viking mine	36.3543, -117.7104			
16ADV02		Talc		Clinochlore, quartz

Allamoore district, west Texas

The ceramic-grade and paint-grade (higher purity) talc bodies currently being mined in the Allamoore district of west Texas were formed by the selective replacement of magnesite. Bourbon (1982, p. 77) suggested: "the [host] magnesite deposits were formed by chemical precipitation in isolated hypersaline lagoons or in associated ephemeral lakes." Desiccation cracks and pseudomorphs of anhydrite and halite, preserved on bedding surfaces in the talcose intervals, indicate the hypersaline depositional environment of the host magnesite. Bourbon (1981, 1982) concluded that Allamoore talc formed via replacement of magnesite by hydrothermal connate or meteoric waters that carried silica in solution.

The Allamoore district presents a dilemma to the otherwise consistent relationships between geologic environment and amphibole content that are described in this paper. The talc bodies that are actively mined in the district are amphibole-free deposits. Yet, an undeveloped prospect on the edge of the district contains talc beds interlayered with long-fiber amphibole asbestos (potassium richterite to potassium winchite, Wylie and Huggins 1980). Microscopic studies of this asbestos deposit by Wylie and Huggins (1980) found that the ends of some of the asbestos fibers were altered to talc forming pseudomorphic fibrous talc, indicating the replacement of asbestos by talc. The amphibole asbestos in this prospect may represent an early fluid event driven by metamorphic processes. In contrast, the amphibole-free talc deposits that comprise the bulk of the district may have formed by a subsequent district-scale hydrothermal event, as suggested by Bourbon (1982). Basic igneous intrusions are exposed within a few talc deposits in the district (Bourbon 1981), perhaps sources of heat and convection for the talc-forming fluids.

Fluid inclusion studies of hydrothermal talc deposits

The geologic literature contains relatively few examples of fluid-inclusion research associated with large (commercial) talc deposits. Especially sparse are fluid-inclusion studies of the major talc bodies in the U.S. Relevant published fluid inclusion data are primarily investigations of deposits described as "hydrothermal talc" that replaced dolostones or magnesite; most of these deposits lack amphibole. Examples are described below.

As noted earlier, analyses of fluid inclusions linked to the large talc deposits of the Ruby and Gravelly Ranges of southwest Montana were recently published. Gammons and Matt (2002) reported analyses and interpretation of fluid inclusions associated with the large talc bodies at the Yellowstone mine, Gravelly Range, Montana. They determined that the talc-forming fluids were brines at 190° to 250 °C containing about 10 wt% NaCl (2.2 m Na^+), 11 wt% $CaCl_2$, and relatively low dissolved CO_2; trapping pressures were estimated at 1–4 kbar. Brady and others (2003) examined the isotope geochemistry of muscovites and fluid inclusions in dolomite and calcite related to the formation of talc bodies in the nearby Ruby Range; they determined the metasomatic fluids were water-rich and CO_2-poor, and that the talc crystallized below ~350 °C.

Large, amphibole-deficient talc deposits at Rabenwald, eastern Alps of Austria, are thought to have formed by saline hydrothermal SiO_2-rich fluids that reacted with magnesite (Moine and others 1989). Fluid inclusions in quartz associated with the talc deposition show a wide range of salinities, with up to 32 wt% NaCl and 3.7 wt% CaCl; analyses indicate that the inclusions were trapped at a minimum of 350 °C and 3 kbar vapor pressure (Pohl and Belocky 1999).

Talc deposits of Puebla de Lillo in northern Spain are replacement bodies in dolostones adjacent to quartzites. Fluid inclusion studies in dolomite and quartz related to the talc deposits, conducted by Tornos and Spiro (2000), suggest the talc-forming fluids were NaCl-$CaCl_2$-rich brines at between 280° and 405 °C with variable salinities (0–23 wt% NaCl eq), under fluid pressures of only 165 to 450 bars. They attribute the dolomitization of pre-existing limestone here and the superimposed talc deposition to be the products of upwelling silica- and Mg-rich brines, heated and convected upward through extensional fault zones by igneous intrusions at depth.

The Mount Bischoff cassiterite-sulfide-rich skarn deposit in western Tasmania replaced a dolomitic horizon. The deposit contains a gangue assembly of quartz, talc, phlogopite, and carbonates. Halley and Walshe (1995) examined the fluid inclusions of this deposit and determined that the talc-bearing assemblage formed from hydrothermal fluids of 320° to 360 °C containing about 2 m NaCl and 1.5 m CO_2. They suggest that an Sn-enriched granite magma at ~1–2 km depth heated and convected the talc-forming fluids.

Several characteristics appear to be consistent within hydrothermal talc deposits, as evidenced by the fluid-inclusion studies described above. The common attributes of hydrothermal talc-forming fluids include: (1) high salinity contents typical of brines (high Na^+ and Ca^+, low CO_2); (2) temperatures below ~400 °C; and (3) trapping pressures below ~4 kbar. The studies described above each suggest that the source of heat and convection

Table 3
Major-element composition (wt%) of: (1) talc ores from the Yellowstone mine, southwest Montana; (2) talc-tremolite ore bodies of the southern Death Valley region, California (Tables 4and 6). Analyses by wavelength-dispersive X-ray fluorescence spectrometry, conducted by Joseph E. Taggart, USGS laboratories in Lakewood, Colorado. See Taggart and others (1981, 1987) for descriptions of methods

Site/sample	Rock type	SiO_2	Al_2O_3	Fe_2O_3	MgO	CaO	Na_2O	K_2O	TiO_2	P_2O_5	MnO	LOI
Yellowstone mine, southwest Montana												
02AYM02	Talc ore	61.9	<0.10	1.54	30.5	0.04	<0.15	<0.02	<0.02	<0.05	0.01	4.90
03AYM02	Talc ore	61.8	<0.10	1.44	30.4	0.08	<0.15	<0.02	0.02	<0.05	0.01	4.99
Talc City district, California												
Talc City mine												
11ADV02	Talc ore	61.6	0.62	1.19	30.5	0.12	<0.15	0.02	0.03	0.05	0.01	5.13
11CDV03	Talc ore	57.5	2.58	1.23	28.2	2.29	<0.15	<0.02	0.19	0.08	0.01	7.45
11FDV03	Talc ore	62.2	0.39	1.12	30.9	0.25	<0.15	<0.02	0.03	<0.05	0.01	5.14
12ADV02	Talc ore	44.6	0.45	0.51	23.2	14.7	<0.15	<0.02	0.03	<0.05	0.03	16.0
Silver Dollar mine												
13ADV02	Talc rock	33.5	4.76	0.36	22.1	18.1	<0.15	<0.02	0.13	0.06	0.02	20.4
Alliance mine												
14ADV02	Talc rock	63.1	0.21	0.59	30.7	0.05	<0.15	<0.02	0.03	0.05	<0.01	4.77
14DDV03	Talc rock	70.8	0.69	0.86	23.2	0.07	<0.15	<0.02	0.07	<0.05	0.01	3.99
Viking mine												
16ADV02	Talc rock	61.7	0.64	1.20	30.6	0.18	<0.15	<0.02	0.04	0.10	0.01	5.09
Southern Death Valley region, California												
Great Wanamingo mine												
07DDV02	Talc ore	54.9	0.52	1.07	26.4	5.95	<0.15	0.02	0.03	<0.05	0.08	9.84
09ADV02	Talc ore	58.9	0.37	0.79	27.6	6.15	<0.15	0.09	0.03	<0.05	0.06	3.73
Grantham mine												
21CDV03	Talc ore	52.2	0.23	0.22	25.9	9.13	0.32	0.20	0.05	<0.05	0.01	11.0
21FDV03	Talc rock	27.6	0.81	0.82	11.9	31.1	0.69	0.49	0.07	<0.05	0.11	26.0
Number 3 workings												
23DDV03	Talc ore	62.1	0.32	0.20	30.9	1.20	<0.15	0.09	0.03	<0.05	0.01	4.67
White Point workings												
23EDV03	Talc ore	54.7	0.35	0.25	26.3	9.48	0.78	0.37	0.04	<0.05	0.02	6.79
23FDV03	Talc ore	56.2	0.44	0.32	27.1	6.98	0.94	0.45	0.05	<0.05	0.02	7.17
Moorehouse mine												
30CDV03	Talc rock	37.2	0.69	0.31	19.0	21.5	<0.15	0.67	0.02	<0.05	0.08	19.7
30DDV03	Talc ore	54.9	0.26	0.23	27.8	6.40	<0.15	0.27	0.03	<0.05	0.03	9.39
30EDV03	Talc schist	42.1	3.80	1.19	20.9	13.1	1.59	3.96	0.10	<0.05	0.05	12.7
30GDV03	Talc ore	57.0	0.73	0.71	25.4	4.92	3.63	1.74	0.05	<0.05	0.02	5.11
Pleasanton mine												
36BDV03	Talc ore	50.9	0.61	0.36	24.0	7.76	<0.15	0.52	0.04	<0.05	0.01	15.0
36DDV03	Talc ore	51.7	0.41	0.37	24.9	10.7	0.91	0.59	0.05	<0.05	0.04	9.89
36EDV03	Talc ore	49.8	0.48	0.29	19.9	10.4	<0.15	0.31	0.03	<0.05	0.02	18.1
Acme mine												
24CDV02	Talc ore	60.3	0.57	0.38	28.4	3.51	0.72	0.32	0.08	<0.05	0.02	4.67
25BDV02	Talc ore	44.8	1.20	0.46	25.0	9.98	0.59	0.93	0.06	<0.05	0.03	16.1
27BDV03	Talc ore	53.9	0.31	0.29	24.6	11.4	0.58	0.24	0.04	<0.05	0.02	7.84
27CDV03	Talc ore	49.8	1.26	1.32	23.2	11.3	1.85	1.09	0.07	<0.05	0.04	8.98
27EDV03	Talc ore	56.9	0.72	0.61	24.9	9.41	2.59	0.43	0.06	0.06	0.03	3.15
27FDV03	Talc ore	55.0	0.51	0.37	25.3	10.5	1.83	0.31	0.05	<0.05	0.03	5.40
Kingston Range												
28ADV02	Talc rock	58.7	0.17	2.95	26.2	6.33	<0.15	0.02	0.07	0.05	0.08	4.30
29ADV02	Talc ore	57.1	0.44	0.34	24.9	11.5	<0.15	0.21	0.05	<0.05	0.03	3.77

LOI, loss-on-ignition; total Fe calculated as Fe_2O_3

Table 4
Names and locations of talc-tremolite deposits sampled by this study within the southern Death Valley region, California. The deposits replaced dolostones along their contacts with intruding mafic sills. The references cited provide descriptions of geology and historic production at these sites, as well as for similar mines and prospects in these areas. The latitude and longitude values were measured by GPS using the North American Datum of 1927, CONUS

District, site name	Latitude, longitude	References
Yucca Grove district		
Great Wanamingo mine	35.4268, -115.8498	Wright and others (1953)
Warm Spring Canyon, Death Valley National Park		
Grantham mine (Big Talc)	35.9611, -116.8955	Wright (1957; 1968); Norman and Stewart (1951); Franklin (1965); Papke (1975b); Evans and others (1976)
Number 3 workings	35.9663, -116.9213	
White Point workings	35.9684, -116.9283	
Ibex Hills, Death Valley National Park		
Monarch mine	35.7767, -116.4083	Wright (1957; 1968); Wright and others (1953); Evans and others (1976)
Moorehouse (Ibex) mine	35.7802, -116.4160	
Pleasanton mine	35.7775, -116.4110	
Alexander Hills, near Tecopa		
Acme mine	35.7682, -116.1275	Wright (1957; 1968); Wright and others (1953)
Kingston Range		
Talcose outcrop	35.7842, -115.9290	Wright (1957; 1968); Wright and others (1953)
Abandoned talc ore pile	35.7900, -116.0000	

that warmed and circulated the talc-forming brines was a buried igneous mass (or masses) with localized hydrothermal fluid circulation assisted by extensional faults that served as fluid conduits. Note that another consistent characteristic of the hydrothermal talc deposits is the absence of amphiboles in the talc ore bodies or wall rocks. In contrast, amphiboles are found to coexist with talc in deposits that formed in higher temperature systems. For example, a fluid-inclusion study was conducted on metasomatic tremolite-talc vein deposits at Campolungo, Switzerland. Here, Walther (1983) analyzed fluid inclusions within thin reaction zones (4 cm in width) between vein quartz and dolomite; the zones contain calcite + tremolite + phlogopite + talc. Walther (1983) determined that the metasomatic fluids were at 500 °C, had an approximate composition of ~5 wt% NaCl and 0.5 mole fraction CO_2, and were emplaced at ~3.25 kbar. A fluid-inclusion study was also performed on the Dongyang talc deposit in Korea by Park and others (1997). They determined that an early event of talc-tremolite replacement of dolomite was due to fluids of ~440–480 °C under ~1.64–2.53 kbar pressure, while a subsequent event of talc deposition that lacked tremolite was due to fluids of ~360–390 °C under pressures of ~1.4–2.2 kbar.
Based on the results of the fluid-inclusion studies described above, it appears that the temperature of ore-forming fluids was an important factor in the presence or absence of amphibole crystallization in the talc bodies. Specifically, talc deposits that formed from fluids of less than ~400 °C, typical of hydrothermal systems, share a distinct absence of accessory amphibole minerals. In contrast, talc deposits formed in higher temperature environments, typical of contact and regional metamorphic settings, consistently contain amphiboles. However, attributing the control on amphibole crystallization to simply the temperature of the fluids may be an oversimplification of these complex ore-forming systems, as is discussed at the end of this paper.

Amphibole-rich talc deposits formed by contact metamorphism

Talc bodies categorized herein as "contact metamorphism" types refer specifically to deposits found in direct contact with an igneous body that are thought to have formed by metasomatism due to the emplacement of that igneous body.

Death Valley region, California

Probably the best examples of talc ore bodies formed within a geologic setting of contact metamorphism are 55 deposits mined and prospected in the southern Death Valley region of California. The mines, most now inactive and (or) abandoned, are clustered in widely separated but discrete districts. Samples were collected from ten of these deposits (Table 4).
The Yucca Grove district, about 29 km northeast of Baker, California, comprises four groups of mines that extracted talc-tremolite rock (Wright and others 1953). The largest operation was the Great Wanamingo mine, consisting of several open-pit workings. The deposits are lens-shaped bodies of massive talc-tremolite rock bounded by a greenish calc-silicate hornfels. Mafic dikes and granitic pegmatites (less than 1 ft thick) also bound the ore zone (chemical compositions shown in Table 5). Thin layers composed of phlogopite, muscovite, and clinochlore formed along the contacts of granitic pegmatites with talc ore. The talc bodies apparently replaced carbonate intervals of a Precambrian-age metasedimentary sequence (Wright and others 1953).
Three samples of friable, massive, white ore material were collected from pit walls of the Great Wanamingo mine, and later analyzed by XRD and SEM/EDS. The samples of ore material contained talc and tremolite, with talc content apparently exceeding tremolite content, and accessory calcite, dolomite, clinochlore, quartz, sepiolite, and kaolinite (Table 6). Asbestiform fibers, with compositions

Table 5
Major-element composition (wt%) of intrusive and dolomitic host rocks associated with talc-tremolite ore bodies of the southern Death Valley region, California (Table 4). Analyses by wavelength-dispersive X-ray fluorescence spectrometry, conducted by Joseph E. Taggart, USGS laboratories in Lakewood, Colorado. See Taggart and others (1981, 1987) for descriptions of methods

Site/sample	Rock type	SiO_2	Al_2O_3	Fe_2O_3	MgO	CaO	Na_2O	K_2O	TiO_2	P_2O_5	MnO	LOI
Southern Death Valley region, California												
Great Wanamingo mine												
07ADV02	Mafic dike	55.5	17.6	8.09	3.16	1.01	2.26	8.71	0.87	0.16	0.07	1.78
07BDV02	Granite dike	70.9	14.4	2.58	1.53	2.88	3.90	1.56	0.45	0.13	0.03	1.36
Grantham mine												
21ADV03	Dol. ls	38.4	8.49	1.81	3.86	21.4	0.77	7.32	0.18	<0.05	0.03	17.3
22ADV03	Gabbro sill	43.2	16.3	15.8	6.17	6.21	3.41	1.02	3.41	0.47	0.18	3.03
21GDV03	Gabbro sill	45.6	14.0	16.2	5.29	4.94	4.63	0.49	4.20	0.71	0.26	3.19
White Point workings												
23GDV03	Gabbro sill	49.6	13.5	13.6	4.24	7.14	5.33	0.40	2.74	1.51	0.24	1.04
Moorehouse mine												
31ADV03	Gabbro sill	43.8	13.4	15.3	8.72	6.51	2.72	1.00	2.20	0.37	0.20	5.20
Pleasanton mine												
36ADV03	Gabbro sill	47.6	14.5	15.2	4.55	6.34	2.39	3.28	2.92	0.57	0.20	2.05
Acme mine												
26BDV02	Dol. ls	57.0	0.21	1.27	8.33	12.7	<0.15	0.10	0.03	<0.05	0.06	19.6
24ADV02	Gabbro sill	45.6	14.7	15.5	6.47	2.69	4.24	3.07	3.72	0.69	0.22	2.70
27DDV03	Gabbro sill	39.5	13.0	14.4	10.6	3.78	2.10	5.82	3.91	0.67	0.14	2.54

LOI, loss-on-ignition; total Fe calculated as Fe_2O_3

compatible with tremolite (by EDS analyses), were found in one of the talc samples (Tables 6 and 7), but were widely scattered.

The Silver Lake mining district consisted of eight talc mines (Wright 1954) about 20 km north-northeast of Baker. Although these were deemed "talc" mines, Wright (1954, p. 13) noted: "tremolite forms an estimated three-fourths of the volume of the bodies." Talc is the next largest ore-body component. The tremolite-talc bodies are hosted by a diopside-feldspar-quartz-calcite hornfels unit, part of a metasedimentary rock sequence thought to be Precambrian in age. The tremolite-talc rock and the hornfels are interpreted to have replaced carbonate rock. Wright (1954) estimated that the mineable bodies range from about 10 to 240 m long and from 1.5 to 4.5 m wide. Wright related the contact metamorphism to the emplacement of large bodies of granitic rocks found near the tremolite-talc bodies. Thin mafic dikes are also found near the borders of several ore zones. Thin laminae of mostly phlogopite are interlayered with the ore body; these laminae often form a selvage along the ore-hornfels contact.

The other 43 tremolite-talc mines of the region lie in mountain ranges that surround the southern half of Death Valley National Park; the talc-bearing belt is about 120 km long by 24 km wide. The geology of the region, the mine sites, and their early mining history are well described by Wright (1968). These deposits are geologically rather similar across the region (Wright 1957, 1968; Evans and others 1976). Thick mafic (gabbroic) sills (Table 5), mostly medium-grained, intruded a siliceous (cherty) dolomitic member of the Proterozoic-age Crystal Spring Formation, forming friable tremolite-talc-rich rock along the sill-carbonate contact zones. The gabbro sills were emplaced during the Mesoproterozoic, based on age determinations by the U-Pb method from baddeleyite crystals in two sills (1,087 ±3 and 1,069 ±3 Ma, Heaman and Grotzinger 1992). The consistent stratigraphic position of the sills at or near the base of the carbonate horizon of the Crystal Spring Formation, but not higher, suggests the sills were emplaced before deposition of the overlying rocks and also indicates that the talc-tremolite deposits are Mesoproterozoic in age.

The tremolite-talc replacement bodies are typically from 150 up to 1,500 m long and 3 to about 30 m thick. The deposits locally contain more tremolite than talc, or more talc than tremolite. SEM observations of the ore material suggest that the tremolite and talc formed by coeval crystallization. Most commonly, acicular amphiboles and platy talc occur intergrown on a microscopic scale (Fig. 1), with only sporadic evidence of talc replacing amphibole.

The largest talc-tremolite mining district of the Death Valley area, and likely the largest producer, was the Grantham-Warm Spring district, which consisted of a series of adits and open pits spread out for just over 3.2 km along Warm Spring Canyon in southwestern Death Valley National Park (Franklin 1965; Wright 1968; Papke 1975b). The second largest mine complex, consisting of adits and large open pits, was the Western-Acme

Table 6
Analyses of talcose samples from talc mines, dumps, and outcrop in the southern Death Valley region, California (see Table 4). For the x-ray diffraction results (see text), "major" minerals are estimated to comprise >25 wt% of the sample analyzed; "minor" minerals form 5–25 wt%; and "trace" minerals comprise <5 wt%

Site name, Sample number	Minerals identified by x-ray diffraction			Amphibole fibers by SEM/EDS
	Major	Minor	Trace	
Great Wanamingo mine				
07DDV02	Talc		Dol, cal, qtz, amph, sep, kaol	Extremely rare
08ADV02	Talc	Cal, amph	Clino, sep, qtz	None were found
09ADV02	Talc	Amph	Cal, qtz, kaol	None were found
Grantham mine				
20ADV03	Talc	Cal	Amph, qtz, phl	Trace
21BDV03	Talc, qtz	Cal	Amph, sep	Trace
21CDV03	Talc	Cal	Amph, vrm	Extremely rare
21FDV03	Cal, talc		Amph, mus, phl, qtz	Trace
Number 3 workings				
23DDV03	Talc		Amph, vrm	Trace
White Point workings				
23ADV03	Talc		Amph, phl, cal, dol	Trace
23BDV03	Talc	Amph	Phl, cal, dol, qtz, sap	Trace
23CDV03	Talc	Amph, cal	Phl, dol, qtz, sap	Trace
23EDV03	Amph, talc	Dol	Mus, qtz, cal, vrm	Trace
23FDV03	Talc	Amph	Qtz, cal, vrm, ant, dol, mus	Extremely rare
Monarch mine				
30ADV03	Talc	Amph, cal	Phl	Trace
30BDV03	Talc		cal, qtz, dol, amph, phl	Trace
Moorehouse (Ibex) mine				
30CDV03	Cal, talc		Mus, amph	Trace
30DDV03	Talc	Cal	Mus, qtz, phl	Trace
30EDV03	Cal, phl	Amph, talc		Trace
30GDV03	Talc, amph		Qtz, dol, mus, cal	Trace
31BDV03	Talc, dol	Phl		Trace
31CDV03	Talc, dol, cal		Amph, phl, sep	Trace
Pleasanton mine				
36BDV03	Talc, dol	Qtz	Mus	Extremely rare
36DDV03	Talc, cal	Amph, mgh	Dol, mus(?)	Extremely rare
36EDV03	Qtz, dol, talc		mus	Trace
Alexander Hills				
24CDV02	Talc		Amph, cal, phl	Trace
24DDV02	Talc, dol	Cal, amph	Phl	Trace
25ADV02	Cal	Talc	Amph, phl	Trace
25BDV02	Talc	Cal, dol, sep	Phl, amph	Extremely rare
26ADV02	Talc	Cal	Amph, phl	Trace
27BDV03	Amph, mgh	Talc, dol	Cal	Trace
27CDV03	Amph, talc, mgh	Qtz, dol	Ant	Extremely rare
27EDV03	Amph, mgh		Talc, cal, mus, ant	Extremely rare
27FDV03	Amph	Talc	Ant, cl-chry, dol, cal	Trace
Kingston Range				
28ADV02	Amph	Talc	Cal, kaol(?)	Trace
28BDV02	Qtz	Amph, talc		Trace
29ADV02	Talc, amph, cal		Qtz, k-spar	Trace

Mineral abbreviations: dol, dolomite; cal, calcite; qtz, quartz; amph, amphibole of the tremolite-actinolite series; sep, sepiolite; kaol, kaolinite; clino, clinochlore; sap, saponite; mgh, ferroan magnesio-hornblende; ant, antigorite; k-spar, K-feldspar; mus, muscovite; phl, phlogopite; vrm, vermiculite; cl-chry, clinochrysotile (best fit identification by mineral structure). Fibrous amphibole particles were identified by visual scans of the sample by SEM and analyses of the particle by EDS (see text); asbestiform amphiboles were described as "trace" in occurrence (a number of fibers, up to 1% by volume but usually less), "extremely rare" (a few fibers found, widely scattered), or "none were found"

mine in the Alexander Hills southeast of Tecopa (Wright 1968).

Samples of talcose rock were collected from abandoned mines, dumps, and outcrops in the southern Death Valley area (Tables 3, 4, and 6). The samples suggest talc is the predominant ore mineral; however, as noted in earlier publications, tremolite is typically a major constituent of these deposits (Fig. 1, Tables 6 and 7). Other major to minor components of the ore material include calcite, dolomite, quartz, phlogopite, magnesiohornblende, and sepiolite (Table 6).

The tremolite particles in the Death Valley ores, as is typical in tremolitic talc deposits, range in habit from blocky to prismatic to acicular to asbestiform, commonly

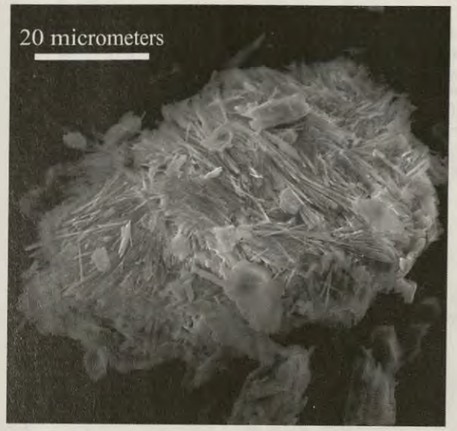

Fig. 1
SEM photomicrograph of a bundle of fibrous tremolite mixed with talc platelets in talc-tremolite ore material from the White Point mine (Table 4), Warm Spring Canyon, Death Valley National Park, California. (Sample 23ADV03, Tables 6 and 7)

within a single sample. Scattered amphiboles in the Death Valley talc deposits occur in asbestiform habits, as bundles of fibers (Figs. 1 and 2) and loose fibers (Figs. 3 and 4). Using SEM/EDS, examination of talc ore samples from the southern Death Valley mines found asbestiform amphiboles in most of the samples. Whereas amphibole particles with prismatic to acicular habits were most common, particles with asbestiform habit (less than 1 μm in diameter, 10 μm and greater in length, curved, splayed ends; Virta 2001) were locally numerous.

In addition to the previously recognized tremolite, EDS analyses indicated that a number of the asbestiform particles in talc ore collected from several mines (Figs. 2, 3, 4, Table 7) have compositions consistent with the sodic-calcic amphiboles richterite and winchite (Leake and others 1997; Wylie and Verkouteren 2000).

A quantitative assessment of the "asbestos" content in the Death Valley talc ores was beyond the scope of this study. The study's SEM/EDS analysis of the mineral residues caused by light handling of the ore samples suggests that prismatic particles are the most common amphibole habit in the talcose rocks. Blocky, prismatic, and acicular examples of the amphiboles in each sample yielded compositions similar to those measured in the fibrous particles (representative fiber compositions shown in Table 7). No obvious correlation between particle composition and morphology was found—tremolite, richterite, and winchite compositions were found in crystals that range from non-fibrous to highly fibrous in habit.

It should be emphasized that the sampling and SEM/EDS studies of these talc deposits were reconnaissance in fashion. Importantly, asbestiform amphiboles in the ore samples were often encountered in SEM scans of the ore material; asbestiform particles locally occur in amounts as high as one percent (by volume), but typically less, in ore samples (described as "trace" in Table 6).

North Carolina deposits

Other examples of talc-amphibole deposits that formed within geologic environments of contact metamorphism occur in western North Carolina; these relatively small talc deposits are spatially and genetically associated with the Day Book dunite body (Murdock and Hunter 1946). Where pegmatites intruded the dunite body, the reaction of magnesian olivine in the dunite with silica in solution formed contact aureoles, which are a several centimeters to a couple of meters thick. The alteration haloes that bound the contacts of pegmatite with dunite contain zones of talc, anthophyllite asbestos, and phlogopite (weathered to vermiculite near the surface) in a serpentine-rich groundmass (Kulp and Brobst 1954).

Talc-amphibole formation in conditions of contact metamorphism

The talc-tremolite deposits of the southern Death Valley-Kingston Range region of California (Wright 1968) were clearly formed by metasomatism caused by intruding gabbro sills. The study samples from inactive talc mines of this region (Tables 3, 4, 5, 6, and 7) represent aspects of these deposits.

Fluid inclusion analyses of the southern Death Valley talc-tremolite deposits have not been performed, so the genetic model presented here is speculative. Wright (1968) determined through field relations that the gabbroic sills intruded the lower and basal horizons of the carbonate section of the late Precambrian Crystal Spring Formation before much of the overlying strata were deposited; he estimated that the overlying sediment load during sill emplacement is now represented by 60 to 760 m of overlying metasedimentary rock. Wright (1968) also suggested that during sill intrusion, the limy strata (now siliceous dolomitic limestone) were poorly consolidated and saturated with water from an overlying sea. Thus, during sill emplacement (and corresponding talc-tremolite deposition) the pore fluids were likely as saline as connate seawater or perhaps more saline. The constituents required to form talc and calcic amphiboles—Si^{4+}, Mg^{2+}, Ca^{2+}, and H_2O—were locally abundant within the contact metamorphic environments associated with the southern Death Valley deposits. A migration of heated silica-rich waters through cherty, dolomitic sediments or rock can explain the coexisting talc-tremolite intergrowths that are common within the Death Valley deposits (Fig. 1). Silica saturation is evidenced by the silicification of the dolomitic limestones that overlie the tremolite-talc deposits (samples 21ADV03 and 26BDV02, Table 5). The gabbroic sills provide an obvious source for the heat and additional silica required to drive these reactions.

Amphibole-rich talc deposits formed by regional metamorphism

Gouverneur district, upper New York State

Talc has been mined for more than a century in the Gouverneur mining district in the western part of

Table 7
Representative cation proportions of fibrous amphibole and platy talc particles as calculated from SEM/EDS analyses of samples from talc-tremolite deposits of the southern Death Valley region, California

Site, Sample no	Fiber shape L x W (μm)	Probable amphibole	Amphibole particle								Talc particle					
			K	Na	Ca	Mn	Fe	Mg	Al	Si	Mg	Fe	Ti	Al	Si	
Great Wanamingo mine																
07DDV02	33.5×1.2	Tremolite	bdl	bdl	1.7	bdl	0.1	5.2	bdl	8.0	3.0	bdl	bdl	bdl	4.0	
Grantham mine																
20ADV03	17.6×0.9	Winchite	0.4	1.0	1.0	bdl	0.2	4.7	0.1	8.1	3.0	bdl	bdl	0.1	4.0	
21BDV03	21.4×0.7	Richterite	0.3	1.4	0.8	bdl	0.3	4.8	0.1	8.0	2.9	bdl	bdl	0.1	4.0	
21CDV03	17.3×1.3	Winchite	0.2	0.7	1.3	bdl	bdl	5.1	bdl	8.1	2.7	bdl	bdl	bdl	4.1	
21FDV03	60.3×0.5	Richterite	0.1	1.9	0.9	bdl	0.3	5.1	0.1	7.8	2.9	bdl	bdl	0.1	4.0	
Number 3 workings																
23DDV03	22.5×1.5	Tremolite	bdl	bdl	1.8	bdl	0.1	5.0	bdl	8.1	3.0	bdl	bdl	bdl	4.0	
White Point workings																
23ADV03	No data	Tremolite	bdl	bdl	1.9	bdl	bdl	4.9	0.2	8.0	3.0	bdl	bdl	0.2	4.0	
23BDV03	56.3×3.4	Tremolite	0.1	0.2	1.6	bdl	bdl	4.9	bdl	8.2	3.1	bdl	bdl	bdl	3.9	
23CDV03	20.5×1.0	Tremolite	bdl	0.2	1.5	bdl	0.1	5.3	0.1	7.9	3.0	bdl	bdl	bdl	4.0	
23EDV03	26.2×0.9	Tremolite	bdl	0.2	1.6	bdl	bdl	5.2	bdl	8.0	3.0	bdl	bdl	bdl	4.0	
23FDV03	9.0×0.6	Winchite	0.1	0.7	1.3	0.1	0.1	5.0	0.1	8.0	3.0	bdl	bdl	bdl	4.0	
Monarch mine																
30ADV03	12.3×0.7	Winchite	0.3	1.1	0.9	bdl	0.6	4.5	0.1	8.1	2.9	bdl	bdl	0.1	4.0	
30BDV03	75.3×2.3	Winchite	0.2	0.9	1.2	bdl	0.2	4.9	bdl	8.0	2.8	bdl	bdl	bdl	4.1	
Moorehouse mine																
30CDV03	25.2×1.8	Richterite	0.3	1.4	1.0	bdl	0.3	4.9	bdl	8.0	2.9	bdl	bdl	bdl	4.0	
30DDV03	31.6×1.4	Richterite	0.3	1.9	0.7	bdl	0.2	5.1	bdl	7.9	2.9	bdl	bdl	0.1	4.0	
30EDV03	60.5×2.0	Winchite	0.4	1.2	0.8	bdl	0.2	5.0	0.3	7.9	2.9	bdl	bdl	0.1	4.0	
30GDV03	44.8×1.6	Richterite	0.1	1.8	0.8	bdl	bdl	5.2	bdl	8.0	3.1	bdl	bdl	bdl	4.0	
31BDV03	18.4×0.8	Tremolite	0.1	0.1	1.7	bdl	0.1	5.1	0.1	8.0	2.9	bdl	bdl	0.1	4.0	
31CDV03	56.7×1.3	Tremolite	0.1	0.2	1.7	bdl	bdl	5.1	bdl	8.0	2.9	bdl	bdl	bdl	4.1	
Pleasanton mine																
36BDV03	29.9×0.5	Richterite	0.1	2.0	0.6	0.1	0.2	5.2	bdl	7.9	2.9	bdl	bdl	bdl	4.0	
36DDV03	26.4×0.4	Winchite	0.2	1.6	0.6	bdl	0.2	5.2	bdl	7.9	2.9	bdl	bdl	bdl	4.1	
36EDV03	34.8×1.6	Richterite	0.2	1.9	0.6	bdl	0.1	5.0	bdl	8.1	2.8	bdl	bdl	bdl	4.1	
Alexander Hills																
24CDV02	22.0×0.8	Tremolite	0.1	0.3	1.6	bdl	bdl	5.1	bdl	8.0	2.9	bdl	bdl	bdl	4.0	
24DDV02	24.5×0.9	Richterite	0.1	2.1	0.5	bdl	0.2	5.1	bdl	7.9	2.9	bdl	bdl	0.1	4.1	
25ADV02	22.4×1.6	Winchite	0.3	0.9	1.0	bdl	0.1	5.1	bdl	8.1	2.9	bdl	bdl	bdl	4.1	
26ADV02	12.9×1.3	Richterite	0.4	1.6	0.9	bdl	0.1	5.2	bdl	7.9	3.0	bdl	bdl	bdl	4.0	
27BDV03	59.0×0.7	Tremolite	bdl	bdl	1.7	bdl	0.2	5.1	bdl	8.0	3.0	bdl	bdl	bdl	4.0	
27CDV03	20.3×0.7	Tremolite	bdl	bdl	1.8	bdl	0.4	5.1	bdl	7.8	3.0	bdl	bdl	0.1	4.0	
27EDV03	24.1×1.0	Tremolite	0.1	0.1	1.9	bdl	0.1	5.1	bdl	7.9	3.0	bdl	bdl	bdl	4.0	
27FDV03	19.6×1.2	Tremolite	0.1	0.2	1.6	bdl	0.1	5.0	bdl	8.0	3.0	bdl	bdl	bdl	4.0	
27FDV03	15.9 x 0.7	Tremolite	bdl	bdl	1.8	bdl	0.1	5.1	bdl	7.9						
Kingston Range																
28ADV02	20.3×1.1	Tremolite	bdl	bdl	1.8	bdl	0.3	5.0	bdl	8.0	2.9	0.1	bdl	bdl	4.0	

Table 7 (Contd.)

Site, Sample no	Fiber shape L x W (μm)	Probable amphibole	Talc particle						Amphibole particle					
			Mg	Ti	Al	Si	Mg	Fe	K	Na	Ca	Mn	Fe	Mg
28BDV02	92.0×1.4	Tremolite	4.9	bdl	bdl	8.1	2.9	0.1	0.1	0.2	1.7	bdl	0.1	4.9
29ADV02	22.9×1.6	Winchite	4.9	bdl	bdl	8.1	3.1	bdl	0.2	0.6	1.4	bdl	bdl	4.9

Sample localities are listed in Table 4. Cation ratios were calculated by stoichiometry using 23 oxygen atoms for amphibole and 11 oxygen atoms for talc. (OH) was assumed to be 2 for amphiboles and talc. The EDS technique cannot distinguish between the oxidation states of Fe (Fe^{3+} versus Fe^{2+}). Most of the amphibole analyzed in this study had negligible Fe; therefore, the oxidation state of Fe would not greatly affect the compositional calculations. Amphiboles are identified as the most likely amphibole species based on semi-quantitative results. Amphibole nomenclature used is based on the recommendations of Leake and others (1997). bdl, below the detection limit of the EDS analytical method

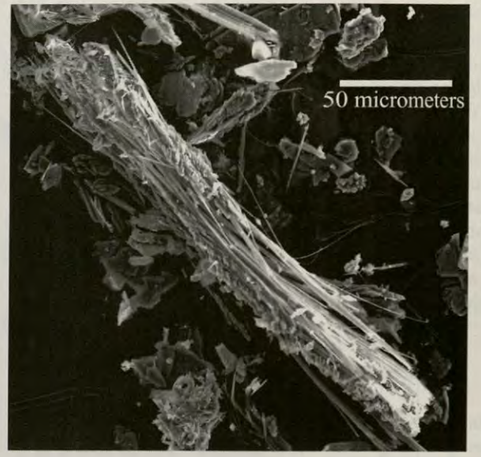

Fig. 2
SEM photomicrograph of a fibrous amphibole bundle (likely richterite) in talc ore material from the Grantham mine (Table 4), Death Valley National Park. Sample collected just inside the ore body within a couple of inches of its outer contact with dolomitic limestone country rock. (Sample 21BDV03, Tables 6 and 7)

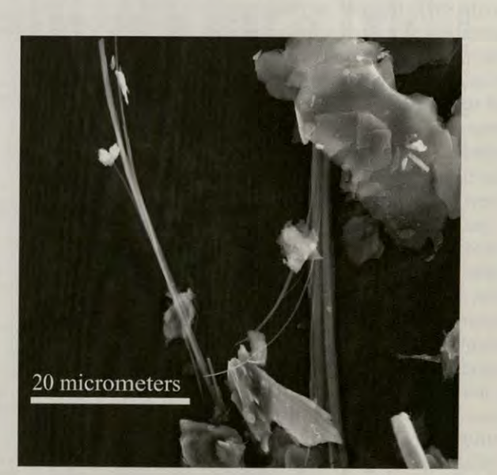

Fig. 3
SEM photomicrograph of asbestiform richterite (?) and platy talc in ore material from the Grantham mine (Table 4), Death Valley National Park. (Sample 21BDV03, Tables 6 and 7)

north-central New York State. These talc deposits replaced dolomitic marble in sinuous belts several kilometers long. The talc-forming event in the district has been interpreted to represent late retrograde metasomatism accompanying significant fluid flow during waning stages of regional metamorphism (Engel 1962). The talcs of the Gouverneur district are often cited as an example of "fibrous talc." Fibrous talc describes talc-rich rocks consisting of an intergrowth of acicular talc (Fig. 5) and

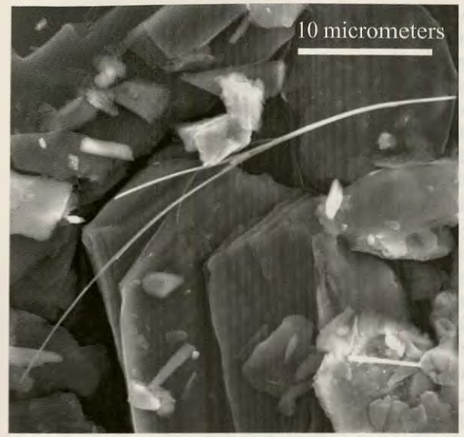

Fig. 4
SEM photomicrograph of platy talc with asbestiform amphibole (winchite?). Coexisting talc and fibrous amphibole are common in the talc deposits formed by contact metamorphism in the southern Death Valley region. This example is from the ore zone of the Acme mine (Table 4) near Tecopa, California (sample 26ADV02, Tables 6 and 7)

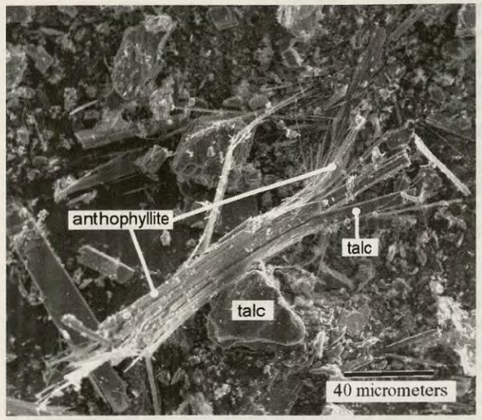

Fig. 6
Example of a "transitional" particle found within a talc deposit formed by regional metamorphism. The particle displays the incomplete replacement of fibrous anthophyllite by talc. This example is from the Gouverneur mining district, north-central New York State. The mineral compositions and identified phases based on stoichiometry at the spots indicated in this SEM photomicrograph were determined by EDS analyses, as shown in Table 8

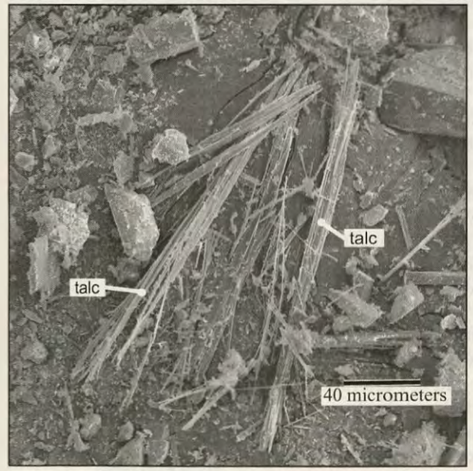

Fig. 5
SEM photomicrograph of fibrous talc within a talc deposit formed by regional metamorphism. This example is from the Gouverneur mining district, north-central New York State. Refer to Table 8 for semi-quantitative (EDS) analyses of these fibers

acicular amphiboles (Goodwin 1974; Greenwood 1998), and commonly includes the pseudomorphous replacement of fibrous amphiboles by talc (Fig. 6); this lends the talcose rock a generally fibrous, rather than massive appearance. The amphiboles intergrown with talc in the Gouverneur deposits are widely but unevenly distributed tremolite and anthophyllite (Engel 1962; Ross and others 1968; Virta 1985; Greenwood 1998). Mn-cummingtonite ("tirodite") is also reported (Ross and others 1968). Overlapping mineral crystallization events, linked to stages of regional metamorphism, are evident in the Gouverneur deposits. The general paragenetic sequence has been determined to involve: (1) formation of acicular tremolite (the primary metamorphic mineral) followed by (2) local replacement by pseudomorphous anthophyllite, followed, during the last stages of regional metamorphism, by (3) replacement of tremolite and anthophyllite by fibrous talc and serpentine (Engel 1962; Ross and others 1968). The resulting deposits consist of fibrous to platy talc, and tremolite, anthophyllite, and minor Mn-cummingtonite in habits ranging from blocky to fibrous. Some amphiboles in the Gouverneur talc ores have been described as "fibrous". When these mineral particles are characterized as asbestos or asbestiform, however, it has led to much debate (Goodwin 1974; Occupational Safety and Health Administration 1992). Much of this controversy is due to inconsistent classification and identification of "cleavage fragments" and "transitional fibers", mineral particles that are common in crushed Gouverneur talc; these particle types are discussed below.

Vermont talc

Talc deposits in Vermont are typical of "black wall" deposits, formed by regional metamorphism and metasomatism of ultramafic rocks, originally composed of dunite or peridotite. These deposits form as zoned alteration "rinds" around ultramafic bodies; the altered zones can be 6.5 km or more long and 460 m wide (Cady and others 1963). The alteration zones are typically comprised of the sequence (Sanford 1982 provides details):

Table 8
Compositions determined for the mineral particles shown in Figs. 5and 6, as compared to the "ideal" compositions of pure talc and anthophyllite. The stoichiometric proportions were calculated from energy dispersive spectroscopy (EDS) analyses

Mineral particle	Normalized cation ratios
Ideal talc	$Mg_3Si_4O_{10}(OH)_2$
Ideal anthophyllite	$(Mg, Fe)_7Si_8O_{22}(OH)_2$ [from $Mg_7Si_8O_{22}(OH)_2$ to approximately $Fe_2Mg_5Si_8O_{22}(OH)_2$]
Fibers in Fig. 5	$(Mg_{2.8}, Al_{0.1}, Ca_{0.1}, K_{0.1})Si_{4.2}[O_{10}(OH)_2]$*
Platy talc, Fig. 6	$(Mg_{2.4}, Ca_{0.1})Si_{4.3}[O_{10}(OH)_2]$*
Talc spindle, Fig. 6	$(Mg_{2.6}, Ca_{0.1})Si_{4.1}[O_{10}(OH)_2]$*
Anthophyllite bundle, Fig. 6	$(Mg_{6.8}, Ca_{0.1})Si_{8.1}[O_{22}(OH)_2]$*
Anthophyllite tuft, Fig. 6	$(Mg_{6.8}, Al_{0.1}, Ca_{0.1})Si_{8.0}[O_{22}(OH)_2]$*

*Cation ratios were calculated by stoichiometry on the basis of 11 oxygen atoms for talc and 23 oxygen atoms for anthophyllite. (OH) was assumed to be 2 for both phases

1. ultramafic rocks, grading to
2. a talc-carbonate-dominant zone, grading to
3. a nearly mono-mineralogical talc zone (often of high purity) several centimeters to meters thick, grading to
4. a calcic amphibole-chlorite-rich zone, grading to
5. a chlorite-rich zone, grading to
6. a transitional mixed zone of altered mafic country rock, grading to
7. the mafic country rock.

Black-wall talc deposits are associated spatially with serpentinite masses that in some areas host well-developed chrysotile asbestos (Bain 1942; Cady and others 1963). The alteration zone locally contains actinolite, tremolite, anthophyllite, and (or) cummingtonite, as described by Cady and others (1963). Zodac (1940, p. 370) described "radiating masses of fibrous actinolite, which often have to be handled carefully as the needle-like crystals may penetrate fingers, are common on the dumps" in a talc quarry near Chester, Vermont. This same deposit yielded three biopyriboles newly recognized and named in the 1970s—jimthompsonite, clinojimthompsonite, and chesterite (Veblen and Burnham 1978). These fibrous amphiboles represent intermediate products of incomplete reactions during the conversion of anthophyllite and cummingtonite to talc (Veblen and Burnham 1978).

Soapstone Ridge, Georgia

As implied by its name, Soapstone Ridge about 13 km south-southeast of Atlanta, Georgia, contains outcrops of impure talc. The deposits formed by regional metamorphism of a large ultramafic body. Analyses of the talcose rock by the U.S. Bureau of Mines (Blake 1982) indicated: (1) mainly prismatic to acicular anthophyllite and cummingtonite, and (2) minor amounts of asbestiform varieties of anthophyllite, cummingtonite, and tremolite in veinlets and fracture fillings.

Dadeville, east-central Alabama

Regional metamorphism and metasomatism of mafic and ultramafic rocks near Dadeville in eastern-central Alabama provide another example of talc-amphibole associations. This elongate, northeast-trending belt of alteration contains discontinuous pods, seams, and lenses of talc (soapstone), talcose-anthophyllite, talcose-pyroxenite, anthophyllite asbestos, and asbestiform tremolite and actinolite in and along the margins of mafic and ultramafic rocks (Neathery and others 1967; Neathery 1968). Anthophyllite asbestos occurs in veins adjacent to talc rock and fills thin (<2.5 cm thick) veinlets that cut the talc bodies. Selective mining of the Dadeville area talc, while also excluding anthophyllite asbestos, may be impossible or at least impractical. In fact, in regard to the Dadeville area deposits, Neathery (1968, p. 2) noted: "Considerable tonnages of anthophyllite asbestos could conceivably be derived as a primary product or as a secondary product from talc mining".

Llano uplift, central Texas

Impure talc deposits (soapstone) occur in a regionally metamorphosed terrane of the Llano uplift of central Texas. At least ten large talc bodies have been identified (Barnes 1943); one small mine in the past produced soapstone used mostly for fireplace and hearth linings. Some of the talc bodies replace calcareous tremolite schists, and thus the talcose rock contains considerable amounts of tremolite, which can exceed the talc component. These tremolite-talc bodies occur in a sequence of talc-chlorite schists, chlorite-epidote schists, amphibolite, hornblende schist, serpentinite masses, gneiss, and sometimes vermiculite deposits (Barnes 1943). The tremolite crystals "vary considerably in shape, some being short and blocky and others being in long thin needles" (Barnes 1943, p. 72). Pockets of tremolite asbestos in schist are mentioned, and serpentinite masses sometimes contain pods of chrysotile asbestos (Barnes 1943). Actinolite is noted in one deposit. Barnes (1943, p. 74) interpreted the formation of these deposits "to be roughly: (1) metamorphism of impure dolomites and limestones into tremolite schist and (2) alteration of the tremolite in part at least to talc". Other talc deposits in the region are anthophyllite-rich and lack tremolite; these talcs also replace schist. The talc-anthophyllite bodies are not so closely spatially associated with serpentine (Barnes 1943).

Complications in evaluating asbestos content

Lending complexity to the determination of the asbestos content in some talc deposits is the presence of amphibole "cleavage fragments" and "transitional fibers". Transitional (dual-phase: talc/amphibole) fibers and cleavage fragments are found as constituents, and sometimes as abundant constituents, of talc ores formed by regional metamorphism. In particular, crushed talc ores extracted from the deposits of the Gouverneur district of upstate New York contain both amphibole cleavage fragments and transitional fibers (Beard and others 2001). Differing interpretation of these particles has caused considerable disagreement over the "asbestos" content of these talc deposits for more than three decades (Goodwin 1974). "Transitional fibers," sometimes termed "intermediate fibers," are composed of fibrous talc and amphibole, in various proportions. They include mineral fibers caught in the act of transformation, such as the incomplete replacement of anthophyllite by talc. X-ray diffraction, optical, and chemical analyses of transitional fibers in many cases either reveal characteristics that range between the ideal values for talc and amphibole or show both the values of talc and amphibole. These transitional fibers may have formed by partial, pseudomorphic replacement of fibrous amphibole by talc and (or) the microscopic intergrowth of amphibole with talc (Virta 1985). For example, in the tremolite-anthophyllite-rich, fibrous talc deposits of the Gouverneur district, Engel (1962) determined that acicular tremolite was the primary metamorphic mineral of the talc ore assemblage, which was replaced locally by pseudomorphous anthophyllite; both tremolite and anthophyllite were subsequently replaced by fibrous talc and serpentine. Where abundant in a talc-amphibole deposit, transitional fibers, such as the example shown in Fig. 6, represent a real challenge to (1) an analyst attempting to quantify the asbestos content of the material, and (2) a toxicologist evaluating the risk potential of the material.

Complexity is added to the analyst's job because, when crushed, amphiboles readily fracture along cleavage planes often forming acicular particles referred to as cleavage fragments. Analytical studies have shown that cleavage fragments of amphiboles display particle populations with distinctive dimensions (shorter particles of lower aspect ratio), which can be distinguished from the longer, thinner, asbestiform particles (Campbell and others 1979; Zoltai 1979; Dorling and Zusmman 1987; Skinner and others 1988; Wylie 1988, 2000). The dilemma of distinguishing cleavage fragments from asbestiform fibers is discussed by Wylie (1988, 2000).

Discussion

A review of published descriptions of about 360 talc deposits (mines, prospects, and occurrences) in the U.S. reveals that a consistent relationship occurs between the primary talc-forming geologic environment and the amphibole content of the talc deposit. That is, talc deposits formed by hydrothermal processes—meteoric or basin brine fluids heated by buried magma bodies—consistently lack amphiboles as accessory minerals. In contrast, talc ores that formed by contact or regional metamorphism are consistently intermixed with amphiboles, sometimes of the asbestiform variety. These consistent associations were confirmed by a limited amount of field and laboratory studies of commercial talc deposits.

Examples of major talc-producing districts formed by hydrothermal processes include those in southwestern Montana (current production; Van Gosen and others 1998), the Allamoore district of west Texas (current production; Bourbon 1982; Kyle and Clark 1990), and the Talc City district, Inyo County, southern California (World War I and II-era mining; Page 1951). Regardless of the source of the hydrothermal fluids (meteoric, basin brine, or perhaps magmatic) or their heat source (buried or distant intrusions), hydrothermal talc deposits are apparently amphibole-deficient bodies. U.S talc deposits described as hydrothermal deposits occur in: Alabama (2 deposits; Blount and Vassiliou 1980; Blount and Helbig 1987); California (31 deposits; Page 1951); Montana (64 deposits; Berg 1979), New Mexico (2 deposits; Kottlowski 1965; Fitzsimmons and Kelly 1980); Nevada (27 deposits; Papke 1975a); Texas (45 deposits; Bourbon 1982); and Washington (1 deposit; McHugh 1985). Descriptions of these hydrothermal talc deposits note only occasional amphibole minerals found in trace amounts, typically as rare components of the dolostone country rock. This study sampled hydrothermal talc of the Talc City district, California, and Yellowstone mine, Montana, and found no amphibole minerals in the ore material. Several published fluid inclusion studies indicate that the hot fluids responsible for "hydrothermal talc" deposits were typically saline (Na^{1+} and Ca^{2+} enriched), and low in CO_2, and had temperatures of less than approximately 400 °C.

Talc formed in geologic settings of contact metamorphism is known in a number of instances to be intergrown with amphibole, some of which is asbestiform. Examples include 55 talc-tremolite deposits of the Death Valley region, southern California, which were developed as mines and prospects during the 20th century. This study sampled ore material from ten of these deposits (Table 4). As described earlier, talc ores from the Death Valley deposits were consistently found to contain asbestiform fibers and fiber bundles of amphiboles (likely tremolite, winchite, and richterite), mixed with platy talc. These talc-amphibole-rich rocks massively replaced cherty dolostones immediately against their contact with intruding gabbroic sills. The Death Valley replacement deposits are essentially a friable rock consisting of mostly talc and tremolite, with either mineral predominant, depending on the site; accessory minerals include calcite, dolomite, quartz, phlogopite, magnesiohornblende, sepiolite, clinochlore, kaolinite, muscovite, and saponite. Talc of mainly platy habit is intergrown and disseminated with amphiboles of prismatic to asbestiform habits in these ore bodies.

More examples of talc deposits formed by contact metamorphism occur in western North Carolina, where they are associated with the Day Book dunite (Murdock and Hunter 1946). Serpentinite formed in contact zones where granitic bodies intruded the dunite mass; these serpentine-rich contact aureoles contain intervals enriched in talc and anthophyllite-asbestos (Kulp and Brobst 1954). Intervals within the alteration contact zones, from several centimeters to a meter thick, are described as "talc-rich" zones and "anthophyllite asbestos" zones, but these descriptions are generalized and not intended to imply asbestos-free

and asbestos-bearing zones that are distinct. The impure talc zones (soapstone) may contain amphiboles, including asbestiform amphiboles, and thus deserve petrologic examination.

Although the talc deposits formed in quite different geologic settings—the Death Valley talcs replaced dolomite and the North Carolina talcs replaced altered dunite—the products of contact metamorphism included amphibole asbestos. Thus, talc deposits formed by contact metamorphism must be regarded as potential sites for amphibole asbestos.

Categorization of talc deposits formed by regional metamorphism appears to be less straightforward than for hydrothermal and contact metamorphic deposits. Amphiboles are ubiquitous in talc deposits formed by regional metamorphism, most commonly as anthophyllite and tremolite-actinolite series minerals. The crystal habits of the amphiboles are quite variable in these metamorphic talc deposits, commonly ranging from blocky to prismatic to acicular to asbestiform within a single outcrop.

The distribution of amphiboles within talc deposits formed by regional metamorphism is also variable between districts. For example, the deposits mined in the Gouverneur mining district in north-central New York State contain an abundance of fibrous talc-amphibole intergrowths that replaced dolomitic marbles (Engel 1962; Ross and others 1968; Virta 1985; Greenwood 1998). The intimate intergrowth of talc and amphibole in the Gouverneur deposits likely formed during retrograde metamorphism in which talc replaced pre-existing amphibole. As a result, talc and amphibole are intermixed in the Gouverneur deposits. In contrast, the "black wall" deposits in Vermont, which formed by regional metamorphism and metasomatism of ultramafic rocks, are zoned deposits in which some of the talc intervals, up to a few meters thick, are often of high purity (Cady and others 1963). The adjacent rock sequence can contain actinolite, tremolite, anthophyllite, and (or) cummingtonite, locally occurring in fibrous habits. These examples from New York and Vermont, as well as talc districts in Georgia, Alabama, and Texas (described earlier), demonstrate that talc deposits formed by regional metamorphism are consistently associated with amphiboles, sometimes with asbestiform habits, but their amphibole distribution is variable and deserves site-specific geologic examination and sampling. Determining the quantity, or actual presence, of asbestiform amphiboles within talc deposits formed by regional metamorphism often produces a variety of estimates by different analysts and by different optical techniques (Wylie 2000). Additionally, amphibole cleavage fragments and transitional fibers lend more complexity to the estimation of asbestos content in crushed examples of these talc ores (discussed above). Variability of amphibole particle size and habit within deposits formed by regional metamorphism has often placed this particular type of talc deposit at the middle of controversies regarding the safety of talc materials. Thus, whereas analysis of amphibole content and character within any particular talcose material is always best done on a site-by-site basis, site-specific analyses are especially advised where the mineral deposit is thought to have formed by regional metamorphic or contact metamorphic processes. The recommendation of techniques for the analyses of amphiboles in talc ores, particularly those formed by regional metamorphism, is beyond the focus and intent of this study; the reader is instead referred to Beard and Rooks (2000).

Conclusions and recommendations

This study revealed that the primary talc-forming conditions—due to hydrothermal processes, contact metamorphism, or regional metamorphism—had a direct influence on the ultimate amphibole content of the talc body. Talc deposits formed by hydrothermal processes—meteoric, basinal brine, or possibly magmatic fluids heated by magma bodies at depth—consistently show negligible amounts or a complete absence of amphibole. Talc deposits that formed in environments of contact metamorphism show a strong tendency to contain asbestiform amphibole within the talc ore. Talc deposits formed by regional metamorphism consistently contain amphiboles, but the amphibole particle habits and sizes are quite variable, requiring careful site-specific study. Given the refocus of attention upon the potential hazards of amphibole asbestos in some industrial mineral deposits, these talc-amphibole relationships may be useful as a first-level screening tool in prioritizing sites for the monitoring or remediation of active and abandoned talc mines.

A review of the fluid-inclusion literature revealed that talc deposits associated with ore-forming fluids cooler than ~400 °C consistently lack amphiboles as accessory minerals. In contrast, talc deposits that formed from higher temperature fluids are typically mingled with amphiboles (Sanford 1982; Walther 1983; Park and others 1997), including amphiboles that in some instances are locally asbestiform. Thus, the fluid temperature(s) of the system may have played an important role in determining the presence or absence of amphibole, and thus amphibole asbestos, within the talc deposit. The geologic environment must play an important role in determining the chemistry and temperature of the talc-forming fluids:

1. hydrothermal talc deposits formed via relatively cool fluids (<400 °C) heated by distant sources, such as buried plutons,
2. contact-metamorphic talc deposits formed against igneous intrusions in localized areas of high temperature conditions, and
3. regional-metamorphic deposits formed in relatively high temperature-pressure environments.

Localized conditions within these talc-forming environments ultimately controlled the deposition or non-deposition of amphiboles and, by association, amphibole asbestos.

The talc-forming systems are complex and fluid temperature alone may not adequately explain talc±amphibole crystallization. Several other parameters should also be considered in system modeling, such as:

1. pressure,
2. the activities of Si, Ca, Mg, and perhaps other chemical components (CO_2) in the system,
3. fluid-flow mechanisms (diffusion, infiltration),
4. the chemical composition of the host rocks,
5. water-rock ratios, and
6. reaction rates.

Reaction-path modeling of these parameters was beyond the current scope of this study. However, mineralogical, chemical, and fluid-inclusion studies are underway at the USGS to better recognize and explain the talc- and asbestos-forming geologic settings, thereby providing insights towards asbestos geology that can be applied to decisions required by land managers, and health and safety administrators.

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Exhibit 9

Bureau of Mines Report of Investigations/1985

The Phase Relationship of Talc and Amphiboles in a Fibrous Talc Sample

By Robert L. Virta

UNITED STATES DEPARTMENT OF THE INTERIOR

Report of Investigations 8923

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UNITED STATES DEPARTMENT OF THE INTERIOR
William P. Clark, Secretary

BUREAU OF MINES
Robert C. Horton, Director

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UNIT OF MEASURE ABBREVIATIONS USED IN THIS REPORT

Å	angstrom	µm	micrometer
ft	foot	wt %	weight percent
min	minute		

THE PHASE RELATIONSHIP OF TALC AND AMPHIBOLES IN A FIBROUS TALC SAMPLE

By Robert L. Virta[1]

ABSTRACT

The Bureau of Mines examined a fibrous talc sample from the Gouverneur talc district in New York by transmission electron microscopy (TEM) and polarized light microscopy to determine the mineralogical relationship of the fibrous talc to the amphiboles present in the sample. Two amphiboles, anthophyllite and tremolite, were present in the sample. Tremolite occurred as a separate mineral phase, which was blocky in habit. Only a few composite tremolite-talc grains were observed. Anthophyllite, however, was present only in the fibrous talc grains. Microdiffraction study of the fibrous talc grains containing anthophyllite showed that the anthophyllite was intermixed with the talc on a fine scale and that there was a crystallographic relationship between the talc and anthophyllite lattices in the fibrous talc grains. A mechanism similar to the process that forms biopyriboles could explain the structural defects, the fibrous habit of the talc, and the structural relationship between the talc and anthophyllite in the fibrous talc grains. Because of these characteristics, phase contrast microscopy and a provisional TEM technique for monitoring asbestos exposure would not distinguish between fibrous talc and fibrous amphiboles. TEM techniques employing electron diffraction and energy-dispersive X-ray analysis are recommended to positively identify the fibrous phases for regulatory purposes.

[1]Geologist, Avondale Research Center, Bureau of Mines, Avondale, MD.

INTRODUCTION

Health scientists are interested in occurrences of amphiboles in talc deposits because of the apparent association between cancer risk and the inhalation of pure amphibole asbestos (21).[2] Among the lesser studied occurrences are the fibrous amphiboles associated with the fibrous talc in the Gouverneur talc district, St. Lawrence County, NY.

Fibrous amphiboles are present in minor amounts throughout deposits in the Gouverneur district. In some localities, they have been altered through metamorphism (5, 8, 19). It is these amphiboles that are associated with fibrous talc (5, 8). Two fibrous talc samples from St. Lawrence County, were found to contain composite talc-amphibole fibers, rather than pure talc. In one case, tremolite occurred with talc; in the other, an unidentified Mg amphibole was present. In both cases, a crystallographic relationship between the talc and amphibole lattices was observed (1, 22). Studies of a partially altered fibrous anthophyllite from Vermont have also shown that chain width disorder and intergrown sheet structures are sometimes found in the amphibole structure (23, 25). Missing structural units were explained as providing sites for ion migration and structural reordering to form the sheet silicate structures from the amphibole double-chain structure (24).

Asbestiform amphiboles, whether occurring with fibrous talc or not, are monitored because of the health risk they pose (4, 9, 14-15). Monitoring is performed using phase contrast microscopy; particles that are equal to or longer than 5 μm and that have a length-to-width ratio greater than 3 to 1 are classified as asbestos (18). When fibrous amphiboles occur with platy talcs, this monitoring process is relatively definitive for asbestos because of the morphological differences. It is when fibrous amphiboles occur with fibrous talc that morphology alone is inadequate to distinguish between phases (16). For this reason, TEM has been recommended for regulatory use. Particle morphology, electron diffraction (ED) and energy dispersive X-ray analysis (EDX) are used to positively identify the particles (6). To provide a relatively rapid analysis for regulatory use, a provisional Environmental Protection Agency (EPA) technique that relies on particle morphology, EDX, and qualitative ED for particle identification was developed (20). In this technique, a 5.3-Å repeat spacing parallel to the long axis of the fiber and an Mg and Si spectrum are used to classify a particle as the amphibole anthophyllite. These characteristics, however, are similar to those of fibrous talc and could result in the misidentification of talc as anthophyllite.

The purpose of this Bureau of Mines study is to determine the phase relationships between the talc and amphiboles present in the sample and examine possible problems that could be encountered in monitoring for asbestos because of the presence of fibrous talc.

ACKNOWLEDGMENTS

The assistance of Dr. A. G. Wylie, crystallography and mineralogy, and C. W. Huggins, X-ray diffraction, both of the Bureau of Mines Avondale Research Center is gratefully acknowledged.

EXPERIMENTAL WORK

SAMPLE AND SAMPLING REGION

The sample selected for this study is a coarsely ground fibrous talc sample from Talcville, St. Lawrence County, NY. The talc deposits in this area consist of lenses of talc interbedded with metasedimentary and metasomatic rocks of the

[2]Underlined numbers in parentheses refer to items in the list of references at the end of this report.

Precambrian Grenville series. Talc, tremolite, anthophyllite, serpentine, chlorite, mica, quartz, and diopside are present in deposits along the talc belt (2-3 5, 8, 13, 19). Most of the talc and the amphiboles formed through the prograde metamorphism of quartzite and dolomite. Anthophyllite and talc have also been reported to have formed through the retrograde alteration of tremolite (19). Engel (8) reported the occurrence of fibrous talc and serpentine which are pseudomorphous after tremolite as a late-stage reaction product of the dynamothermal metamorphism of the region. Stemple (22) examined one sample of talc from St Lawrence County by electron microscopy and reported the occurrence of fibrous talc-tremolite particles. They observed a crystallographic relationship between the fibrous talc and tremolite. Barr (1) reported the presence of amphibole-talc particles in a talc sample from St. Lawrence County. The amphibole was identified only as a Mg-rich monoclinic amphibole.

The sample used in this study was randomly selected. Consequently, it may not be representative of the morphology or the morphological characteristics of particles in the entire deposit.

SAMPLE PREPARATION

Samples were prepared for X-ray diffraction analysis (XRD) by freezer milling to minus 325 mesh and briquetting in a pellet press. Quartz present in the sample was used as an internal calibration standard.

Samples for infrared spectrophotometric analysis (IR) were prepared by freezer milling to minus 325 mesh and mixing 2 mg of sample in 200 mg of KBr powder in a mixer mill. Pellets were made in a vacuum press under 9 tons of pressure for 2 min.

Samples for TEM analysis were ground and suspended in water with sonification. A drop of the suspension was placed on a collodian-coated TEM grid, dried on a hotplate, and carbon-coated in a vacuum evaporator.

ANALYSIS AND RESULTS

Talc, quartz, tremolite, phlogopite, and carbonate were identified by polarized light microscopy (PLM). Talc is the major phase with 1 to 3 wt % quartz and 1 to 3 wt % tremolite present. Phologite and carbonate were trace constituents. Talc particles had lengths ranging from 5 to several hundred micrometers. The particle morphology of the talc ranged from platelets to individual fibers to fiber bundles with splayed ends (fig. 1). The

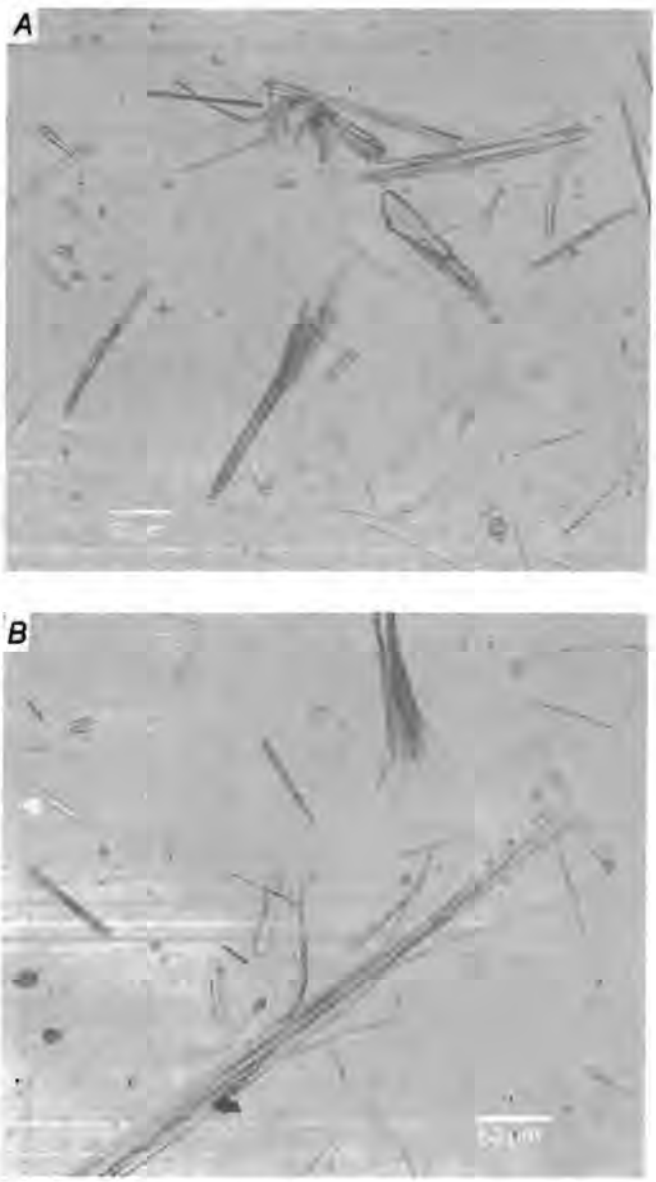


FIGURE 1. - *A*, Variation of particle sizes and shapes in the talc sample, including platelets and fiber bundles of talc; *B*, talc fiber bundles splaying into thin talc fibrils.

quartz and tremolite had particle sizes of 10 to 150 μm. Quartz grains were generally anhedral and often contained inclusions of fibers. The tremolite was present in a blocky habit with a few prismatic grains. Several tremolite particles had partially altered to talc, forming composite talc-tremolite grains similar to those described by Wright (27). No gradations in the refractive indices between minerals were observed in these composite grains or in the fibrous talc particles. Gradations in the refractive indices have been reported in particles where amphibole are altering to talc (1).

Talc, quartz, tremolite, anthophyllite, and phlogopite were identified using XRD (table 1). Slightly less than 5 wt % anthophyllite was estimated to be present using mixed standards. Tremolite, whose major peak intensities were less than those of anthophyllite, was present in lesser concentration than anthophyllite. The maximum concentration of 5 wt % for anthophyllite was verified using mixed standards for IR analyses.

TABLE 1. - Powder X-ray diffraction data, briquetted fibrous talc

hkl	2θ[1]	d_{obs}	d_{111}[2]	I	Other minerals
	8.83	10.014		45	Phlogopite.
002	9.44	9.368	9.34	>100	Talc.
	10.53	8.400		20	Tremolite.
	10.70	8.267		8	Anthophyllite.
	17.66	5.021		6	Phlogopite.
004	18.96	4.680	4.66	85	Talc.
020	19.40	4.575	4.55	20	Talc.
	20.85	4.260		25	Quartz.
	21.11	4.208		5	Tremolite.
	26.66	3.344		>100	Quartz.
	27.23	3.274		6	Tremolite
	27.65	3.226		12	Anthophyllite.
006	28.60	3.121	3.116	>>100	Talc.
	29.33	3.044		64	Anthophyllite.
	31.92	2.803		8	Tremolite.
	32.64	2.743		7	Anthophyllite?
	35.30	2.542		3	Anthophyllite.
	35.76	2.510		4	Phlogopite.
132	36.18	2.482	2.476	3	Talc.
	36.55	2.458		20	Quartz.
008	38.46	2.340	2.335	11	Talc.
	38.83	2.319		3	Tremolite or anthophyllite.
	39.48	2.282		8	Quartz.
	40.31	2.237		6	Quartz.
	42.47	2.128		8	Quartz.
	45.14	2.008		14	Phlogopite.
	45.81	1.980		7	Quartz.
	48.13	1.890		18	Tremolite.
0·0·10	48.61	1.872	1.870	35	Talc.
	49.38	1.845		6	Anthophyllite?
	50.20	1.817		20	Quartz.
	54.91	1.672		11	Quartz.
313	58.20	1.585		22	Talc?

See footnotes at end of table.

TABLE 1. - Powder X-ray diffraction data, briquetted fibrous talc--Continued

hkl	2θ[1]	d_{obs}	d_{lit}[2]	I	Other minerals
0•0•12	59.20	1.560	1.557	16	Talc.
	60.03	1.541		24	Quartz.
060, $33\overline{2}$	60.68	1.526	1.527	17	Talc.
062, 330	61.68	1.503	1.509	6	Talc.
	64.88	1.437		2	Tremolite.
	67.80	1.382		15	Quartz.
	68.20	1.375		25	Quartz.
	68.36	1.372		19	Quartz.
	68.50	1.369		4	Unidentified.
	69.38	1.354		11	Talc?
0•0•14	70.33	1.338	1.336	14	Talc.
260	71.43	1.320	1.317	4	Talc.
	73.53	1.288		4	Quartz.
	75.73	1.256		7	Quartz.
	77.73	1.228		4	Quartz.
	79.96	1.199		5	Quartz.
	80.75	1.190		4	Unidentified.
	81.13	1.183		5	Quartz.
	81.53	1.180		8	Quartz.
	83.88	1.153		3	Quartz.

[1]Naturally occurring quartz found in talc fibers used as internal standard for minor 2-theta corrections.
[2]Values from JCPDS card 13-558.

Based on the results of the PLM, XRD, and IR analyses, the sample is estimated to be composed of greater than 90 wt % talc, 3 to 5 wt % anthophyllite, 1 to 3 wt % tremolite, 1 to 3 wt % quartz, and trace amount of phlogopite and a carbonate.

Although tremolite and anthophyllite were detected by XRD, only tremolite was observed by PLM. This suggests that anthophyllite is closely associated with the talc on a submicroscopic scale. Electron microscopy (EM) further confirmed this relationship of the anthophyllite to the talc. The morphological characteristics observed by PLM were observed by TEM on particles whose size was below the resolution limit of PLM (fig. 2). Both platy and fibrous particles were observed. Several fiber bundles composed of fine fibrils were also present. The individual fibrils are approximately 1,000 Å wide.

Identification of the individual fibers was performed using selected area electron diffraction (SAED) and EDX. The SAED spot patterns for various particle orientations of talc, tremolite, and anthophyllite were plotted using the reflection conditions specified in the

FIGURE 2. - Fibrous talc particle pseudomorphic after anthophyllite. Note the narrow fibrils of talc separating from the particle.

International Tables for X-ray Crystallography (10). These predicted SAED patterns and calculated d spacings were then used to identify the mineral phases. For tremolite, the body-centered cell described by Warren (26) was used to determine reflection conditions.

All fibrous particles were identified as either talc or talc-amphibole particle using SAED and EDX. Figures 3 and 4 show an elongated talc particle and a fibrous talc-amphibole particle respectively. The talc is oriented with its b*

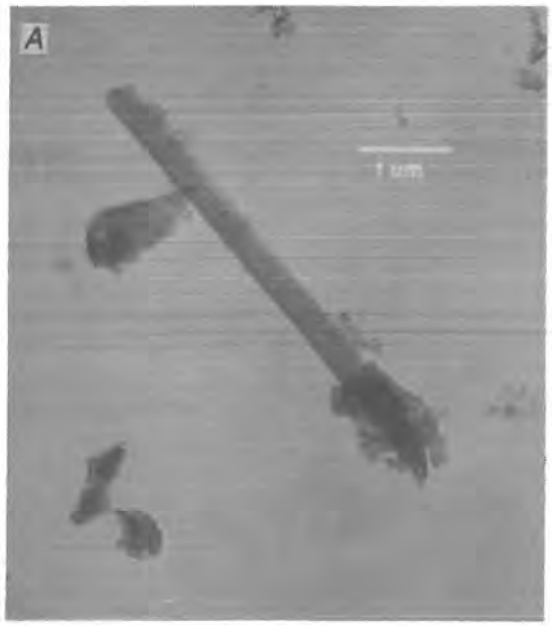
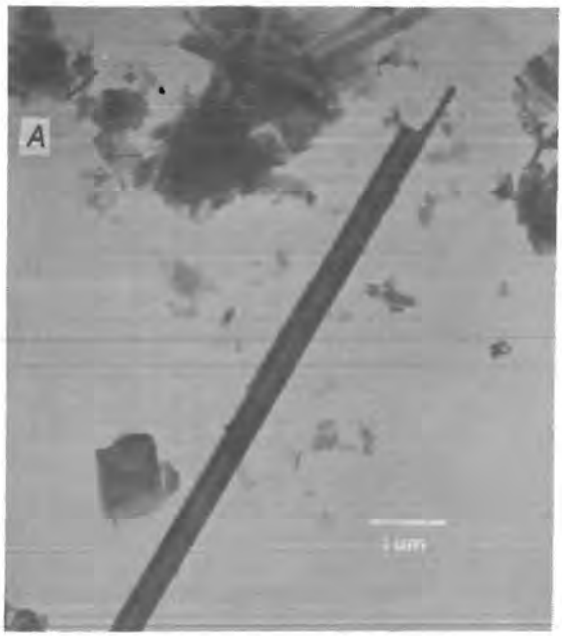


FIGURE 3. - *A*, Fibrous talc particle; *B*, corresponding SAED pattern with a* oriented parallel to the particle length and b* oriented perpendicular to the particle length (TEM photomicrographic).



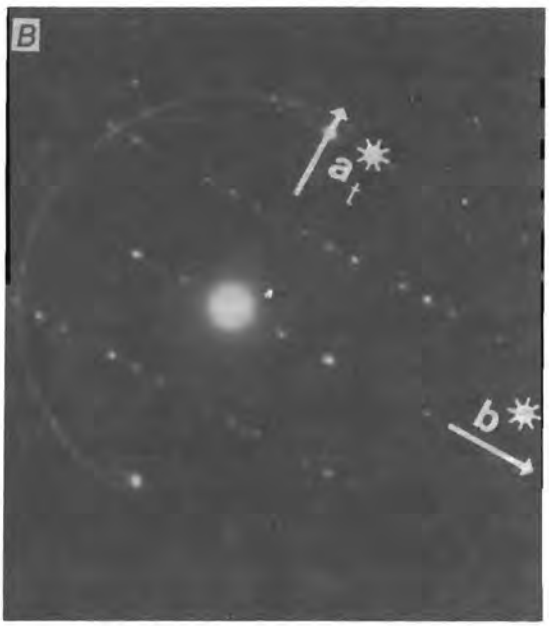


FIGURE 4. - *A*, Fibrous talc-amphibole particle; *B*, corresponding SAED pattern with a* (talc) and c* (amphibole) parallel to the particle length and b* (talc) and b* (amphibole) perpendicular to the particle length (TEM photomicrographic).

direction perpendicular to the length of the fiber and its a* direction parallel to the fiber length (fig. 3*B*). For talc-amphibole particles, the amphibole ED pattern is superimposed on the talc pattern (fig. 4*B*). The amphibole is oriented with the c* direction parallel to the fiber length and b* perpendicular to the fiber length. This ED pattern is shown schematically in figure 5, where the b* talc axis is parallel to the b* amphibole axis and the a* talc axis is parallel to the c* amphibole axis. The a* amphibole axis and c* talc axis were parallel to the electron beam. Dominant orientation of the (100) amphibole face perpendicular to the electron beam has been reported in the literature for amphibole asbestos (17). The maximum crystal growth of the fibrous talc is along the a axis with limited growth along the b axis and c axis. In platy talcs, the a and b lattice directions usually have equivalent crystal growth (7).

Many of the fibrous talc-amphibole particles exhibit a streaking of the ED pattern in the b* (amphibole) direction, suggesting possible defect structures in the b* lattice direction (fig. 4*B*). Other fibrous particles displayed distinct ED spot patterns, indicating that structural defects were minimal. These generally exhibited only a talc ED pattern.

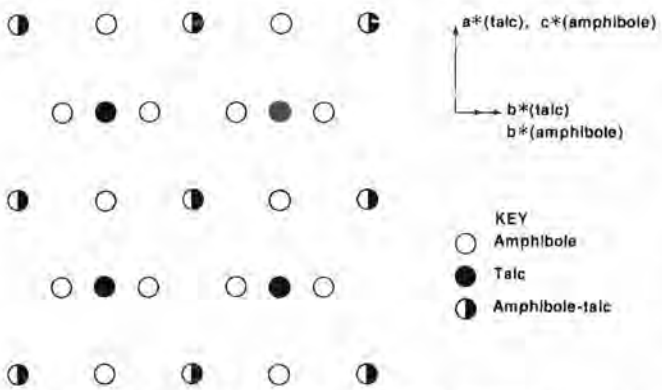


FIGURE 5. - Representation of superimposed talc-amphibole reciprocal lattices show in figure 4*B*. a* (talc) is parallel to c* (amphibole), and b* (talc) is parallel to b* (amphibole). b* (talc) ≈1/2 b* (amphibole).

Microdiffraction (μD) was used to determine if the mixed talc-amphibole ED pattern observed using conventional SAED could be attributed to alteration on a submicroscopic scale or partial alteration of an entire portion of the individual fibrous grains. Microdiffraction images were observed using a nominally rated 200-Å-diameter electron beam in the scanning transmission electron microscope mode along both the length and the width of the particles. Most of the fibrous particles exhibited either a talc μD pattern or a mixed talc-amphibole μD pattern. Only a few fibrous particles exhibited a mixed talc-amphibole μD pattern in one portion of a grain and a talc μD pattern in another portion of the same grain. No fibrous particles exhibited only an amphibole μD pattern.

Approximately 50 fibrous particles were examined qualitatively using EDX and found to be composed primarily of Mg and Si. Less than 2% of the particles contained any Ca or Fe, suggesting that tremolite is a minor to trace phase and that anthophyllite is the predominant amphibole. Semiquantitative EDX analyses were performed on particles with thicknesses less than approximately 1 μm using the Cliff-Lorimer technique (11). A pure Italian talc sample was used as the EDX standard. The Italian talc was composed of 19.8 wt % Mg and 29.0 wt % Si as determined using wet chemical techniques. Accuracy of the Cliff-Lorimer technique was approximately ±5 wt % relative under the operating conditions used in this study. A 4.5 wt % water content of the talc was assumed.

The fibrous particles ranged from 18.2 to 21.2 wt % Mg with an average value of 20.4±0.6 wt %. Silicon ranged from 27.9 to 30.6 wt % with an average value of 28.9±0.6 wt %. No Fe was detected. Several blocky particles exhibited EDX spectra similar to that of tremolite.

The percentage of amphibole in each fibrous particle could not be determined accurately using EDX because of the similarity of the Mg and Si content of the

talc and amphiboles. The particles would have to contain approximately 40 wt % anthophyllite before any significant shift in talc composition would be observed using semiquantitative techniques. The presence of more than 5 wt % tremolite would be detected because of the presence of Ca in the EDX spectrum. No significant variations in elemental concentrations (less than 2 wt %) were detected in different portions of most analyzed grains.

DISCUSSION

The intergrowth of talc with amphiboles, serpentine, chlorite, mica, and pyroxenes has been reported in several papers (1, 22-23, 25). The crystallographic relationship between the amphibole and fibrous talc in the sample examined is similar to that observed by Stemple (22), except that anthophyllite and possibly tremolite is intergrown with talc rather than only tremolite. Since both tremolite and anthophyllite are found in talc deposits and retrograde alteration of amphiboles has been reported in geological studies of the sampling area, the alteration of either mineral to fibrous talc could be expected.

Within the fibrous portion of the sample, the EDX and ED data indicate that no amphiboles occur as a free phase and that amphiboles occur only as composite talc-amphibole grains. The amphibole structures were determined to be interspersed on an extremely fine scale (several hundred angstroms in width) using μD and EDX. In all cases, either talc or superimposed talc and amphibole diffraction patterns were observed. No diffraction patterns and EDX spectra corresponding to a pure amphibole phase were observed. Had the composite particles been composed of coarse lamallae of talc and amphibole or had partial alteration of an entire portion of a grain occurred, only ED patterns and EDX spectra typical of an amphibole would have been observed.

Veblen (25) describes structural defects in pyroxenes and amphiboles which are believed to contribute to the alteration of their chain structures. The missing structural units were explained as providing sites for ion migration and structural reordering in the amphibole to form the sheet structure (24). Similar structural changes are likely to have been involved in the alteration of the amphibole to fibrous talc. The crystallographic relationship between the fibrous talc and amphibole and the fine intermixing of the two minerals are consistent with such an alteration mechanism. Defect structures in the lattice structure parallel to the b* direction of amphibole suggested by the streaking observed in the ED patterns are also consistent with the chain width disorder of chain silicate alteration described by Veblen (25).

A positive identification of the amphibole within the talc fibers could not be made by EM because all fibers had their a axis of amphibole parallel to the electron beam and the a* spacing was not determined. Tilting of the sample through angles of ±25° had almost no effect on the ED pattern. This phenomenon is explained as a result of the ED formation process related to the particle thickness (12). However, the data indicate that anthophyllite, rather than tremolite, is the major amphibole occurring in the fibrous talc grains. The 1 to 3 wt % nonfibrous tremolite observed as a free amphibole phase by PLM represents the bulk of the tremolite in the sample. Intermixing of the anthophyllite with talc fibers could account for its not being observed as a free amphibole phase by PLM despite its presence in the sample in greater quantities than tremolite. This also suggests that the fibrous talc and fibrous talc-anthophyllite particles formed from anthophyllite. Further, the fibril dimensions and dominant (100) orientation of the amphibole lattice, similar to what would be observed with asbestos, suggest that the fibrous morphology is due to the alteration of fibrous, if not asbestiform, anthophyllite. The dominant (001) crystal face of the talc would be developed in the alteration products due to the nature of the alteration process.

Based upon the results of this study and of studies on fibrous talc from other regions of the Gouverneur talc district, fibers of talc or talc-amphibole composites could be expected as a result of the alteration of fibrous amphiboles. This is one area of consideration when regulating for asbestos in talcs. The current phase contrast technique for asbestos monitoring uses the criteria of length equal to or greater than 5 μm, aspect ratio equal to or greater than 3 to 1, and parallel sides for classifying particles as asbestos. Many of the fibrous talc particles observed would meet these criteria, so other means of evaluating air monitoring filters would be required in these cases. Individual fibers could be positively identified with TEM using particle morphology, ED, and EDX. The use of ED, however, requires photographing and indexing each ED pattern. For regulatory purposes, a more rapid TEM technique would be required to permit analysis of large numbers of samples. A proposed technique using ED and the 5.3-Å repeat spacing would be appropriate if fibrous talc was not present. The 5.3-Å c spacing is very similar to the 5.28-Å a spacing observed on the fibrous talc grains, and both are oriented parallel to the fiber length. The 5.28-Å spacing would be indistinguishable from the 5.3-Å spacing for amphiboles using qualitative techniques. The particle morphology and the Mg and Si composition are similar to those of fibrous anthophyllite. To increase the accuracy of this technique, the spacings perpendicular to the 5.3-Å spacing should be determined. Assuming that most fibrous talc grains would lie on the 00ℓ face as they were in this study, the 18-Å b spacing of amphiboles would be distinguishable from the 9-Å b spacing in talc. On grains without this orientation, the more thorough quantitative ED technique would be required. An accurate assessment of whether fibrous talc should be suspected to be present in the sample prior to TEM analysis could be accomplished by determining the mineralogy through PLM and XRD.

CONCLUSIONS

The fibrous talc sample contained talc, anthophyllite, tremolite, quartz, and carbonate. Anthophyllite is present only within the fibrous talc grains. The intermixing of the talc and anthophyllite on a submicroscopic scale and the crystallographic relationship between the talc and anthophyllite crystal lattices suggest an alteration mechanism similar to that observed in the formation of some biopyriboles. Tremolite, however, was observed as a physically distinct nonfibrous amphibole phase, and little, if any, was present within the fibrous talc grains. The fibrous morphology, the lattice relationships in the talc-anthophyllite intergrowths, and the dominant (100) orientation of the amphibole lattice are suggested to result from alteration of fibrous or asbestiform anthophyllite. The possible presence of fibrous talc in samples containing fibrous amphiboles suggests that phase contrast microscopy and qualitative TEM techniques alone may be inappropriate for the regulation of amphibole asbestos in talcs. These techniques would not positively distinguish between amphiboles and fibrous talc because of the characteristics of the fibrous talc resulting from the alteration of fibrous amphiboles.

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